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Clean Revised Manuscript

Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project

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Drafting of the work: MD, AL, JFSM, MB, and PS.
Critical revision of the work for important intellectual content: all authors.
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Final approval of the version to be published: all authors.
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

Data Sharing

After the publication of this article, data collected for this analysis and related documents will be made available to others upon reasonably justified request, which needs to be written and addressed to the attention of the corresponding author Dr. Mattia D'Agostino at the following e-mail address: mattia.dagostino[*at*]unito.it. The HARMONY Alliance, via the corresponding author Dr. Mattia D'Agostino, is responsible to evaluate and eventually accept or refuse every request to disclose data and their related documents, in compliance with the ethical approval conditions, in compliance with applicable laws and regulations, and in conformance with the agreements in place with the involved subjects, the participating institutions, and all the other parties directly or indirectly involved in the participation, conduct, development, management and evaluation of this analysis.

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- Poster presentation, European Hematology Association (EHA) 2020 25th Congress, Jun 11-21, 2020. D'Agostino, M., Lahuerta, J. J., Waage, A., Bertsch, U., Zamagni, E., Mateos, M.-V., … Sonneveld, P. A New Risk Stratification Strategy in Newly Diagnosed Multiple Myeloma: An Analysis on Mature Data From European Clinical Trials Within the HARMONY Big Data Platform. HemaSphere, 4(S1), 421-422 [Abstract #EP933], 2020.
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ABSTRACT

Purpose. Newly diagnosed multiple myeloma (NDMM) patients show heterogeneous outcomes, and ~60% of them are at intermediate-risk according to the Revised International Staging system (R-ISS), the standard-of-care risk stratification model. Moreover, chromosome 1q gain/amplification (1q+) recently proved to be a poor prognostic factor. In this study, we revised the R-ISS by analyzing the additive value of each single risk feature, including 1q+.

Methods. The European Myeloma Network, within the HARMONY project, collected individual data from 10843 NDMM patients enrolled in 16 clinical trials. An additive scoring system based on top features predicting progression-free (PFS) and overall survival (OS) was developed and validated.

Results. In the training set (n=7072), at a median follow-up of 75 months, ISS, del(17p), LDH, t(4;14), and 1q+ had the highest impact on PFS and OS. These variables were all simultaneously present in 2226 patients. A value was assigned to each risk feature according to their OS impact (ISS-III 1.5, ISS-II 1, del(17p) 1, high-LDH 1, and 1q+ 0.5 points). Patients were stratified into 4 risk groups according to the total additive score: low (R2-ISS-I, 19.2%, 0 points), low-intermediate (II, 30.8%, 0.5-1 points), intermediate-high (III, 41.2%, 1.5-2.5 points), high (IV, 8.8%, 3-5 points). Median OS was not reached vs. 109.2 vs. 68.5 vs. 37.9 months, and median PFS was 68 vs. 45.5 vs. 30.2 vs. 19.9 months, respectively. The score was validated in an independent validation set (n=3771, 1214 of whom with complete data to calculate R2-ISS) maintaining its prognostic value.

Conclusions. The R2-ISS is a simple prognostic staging system allowing a better stratification of intermediate-risk NDMM patients. The additive nature of this score fosters its future implementation with new prognostic variables.

CONTEXT SUMMARY

Key objective. The European Myeloma Network, within the HARMONY project, collected data from 10843 newly diagnosed multiple myeloma (NDMM) patients to propose a second revision (R2-ISS) of the current Revised International Staging System (R-ISS; Palumbo et al. JCO 2015). The top features predicting overall survival (OS) and progression-free survival (PFS), including 1q gain/amplification (1q+), were used to develop and validate an additive risk score.

Knowledge generated. The impact on OS of ISS, del(17p), LDH, t(4;14), and 1q+ was used to define R2-ISS. Four risk groups predicting different OS and PFS rates were identified: low (R2-ISS-I, 19.2%), low-intermediate (II, 30.8%), intermediate-high (III, 41.2%), high (IV, 8.8%).

Relevance. R2-ISS is a new staging system allowing a better stratification of intermediate-risk NDMM patients, as compared to R-ISS. R2-ISS incorporated 1q+ to the standard variables used to stratify the risk of NDMM patients, and its additive nature fosters future implementations with new prognostic factors.

Original report

INTRODUCTION

Multiple myeloma (MM) is a hematologic disease with heterogeneous outcomes and is associated with survival rates ranging from few months to more than a decade.[1] In 2015, the Revised International Staging System (R-ISS) was introduced to develop a robust prognostic system based on widely available biomarkers that is now considered a standard risk stratification model for newly diagnosed (ND)MM patients.[2,3]

The R-ISS takes into account ISS (which integrates β2-microglobulin levels and serum albumin to reflect tumor mass and renal function),[4] high-risk chromosomal abnormalities (CA) detected by interphase fluorescence in situ hybridization (FISH) [deletion(17p), translocation t(4;14)(p16;q32), or t(14;16)(q32;q23)],[5] and serum lactate dehydrogenase (LDH) levels.[6,7] The R-ISS identifies 3 groups: R-ISS I including ISS I without neither high-risk CA nor high LDH levels; R-ISS III including ISS III and either high-risk CA or high LDH level; and R-ISS II including all the other possible combinations. At a median follow-up of 46 months, median overall survival (OS) was not reached (NR) in the R-ISS I, 83 months in the R-ISS II, and 43 in the R-ISS III group, respectively.[2]

The main limitation of the R-ISS was that 62% of patients were classified into the intermediate-risk category (R-ISS II), possibly including patients with different risk levels of progression/death.

Recently, 1q gain (3 copies of 1q) or amplification (≥4 copies of 1q), which were not included in the R-ISS, proved to be independent poor prognostic factors in NDMM.[8–10] Moreover, in the R-ISS, high-risk CA were considered as present if at least one among del(17p), t(4;14), or t(14;16) was detected, while emerging data showed that having more than one high-risk CA predicted poorer outcomes.[8]

The European Myeloma Network (EMN), under the umbrella of the European Union-funded HARMONY project,[11] collected individual patient data from a large cohort of young and elderly NDMM patients to improve risk stratification and propose a revision of the current R-ISS, which is here referred to as "Second Revision of the ISS" (R2-ISS). In this work, we analyzed the prognostic value of each single baseline risk feature in an additive fashion, including 1q gain/amplification in the risk calculation.

PATIENTS AND METHODS

Patients

In this analysis, we included 10843 NDMM patients who were enrolled in 16 international, multicenter clinical trials from 2005 to 2016 and met the data quality requirements (see the *Supplementary Appendix* and *Table S1*). Results of the included trials were previously reported (IST-CAR-506[12], EMN01[13,14], RV-MM-EMN-441[15], MM-RV-PI-209[16], RV-MM-PI-114[17,18], GIMEMA-MM-03-05[19,20], 26866138MMY2069[21], HOVON-65/GMMG-HD4[22,23], MM-BO2005[24,25], GEM05MENOS65[26,27], EMN02/HO95[28,29], GEM05MAS65[30–32], GEM2010MAS65[33], HOVON-87/NMSG-18[34], GMMG-MM5[35,36], and NCRI MYELOMA XI[37–41]). Written informed consent was given before entering the source trials, which were approved by the institutional review boards and ethics committees at each of the participating centers and conducted in accordance with the Declaration of Helsinki. After the acquisition of data from the source trials, all patient data were de-facto anonymized[42] in compliance with the General Data Protection Regulation (GDPR), harmonized and transformed using an Observational Medical Outcomes Partnership (OMOP) Common Data Model,[43] and eventually registered in the HARMONY Big Data Platform.

During their upfront treatment, all patients received at least an immunomodulatory drug (IMiD) and/or a proteasome inhibitor (PI) during the induction or consolidation/maintenance phases (*Table S2*).
The collected baseline data and the definition of each variable are available in the *Supplementary Appendix*.
OS was the primary endpoint and was defined as the time from symptomatic MM diagnosis until death due to any cause or until the last date the patient was known to be alive. Progression-free survival (PFS) was the secondary endpoint and was defined as the time from symptomatic MM diagnosis until progression or death due to any cause, or until the last date the patient was known to be alive and free of progression.

CA detection
Bone marrow plasma cells (BMPCs) were enriched using a CD138-directed enrichment, and CD138+ BMPCs were analyzed by FISH as previously described[2,9] (training set) or by molecular methods validated against FISH[8] (validation set, see the *Supplementary Appendix*). Data about the presence of the following CA were acquired at baseline: del(17p), gain/amp(1q21), t(4;14)(p16;q32), and t(14;16)(q32;q23). Since data about the number of nuclei with 3 (gain) or ≥4 (amp) copies of 1q21 were not available, gain or amp(1q21) were grouped together regardless of copy numbers of the gained region and were indicated with the symbol 1q+.[44]
Patients were considered positive for each CA when its percentage was higher than a cut-off threshold defined by each local laboratory. Details about cut-off variability among laboratories are reported in the *Supplementary Appendix*.

Statistical analysis
Patients were analyzed on an intention-to-treat basis.
The patient population was divided into a training set (7072 patients enrolled in 15 clinical trials) and a validation set (3771 patients treated in the NCRI Myeloma XI trial; *Table 1*). The NCRI Myeloma XI trial was included in the HARMONY Data Platform as an external validation set on June 23, 2021, when the training set[45] had already been developed. NCRI Myeloma XI enrolled both transplant-eligible (TE) and transplant-ineligible (NTE) patients (*Supplementary Appendix*).
OS and PFS were estimated by the Kaplan-Meier method and analyzed with the Cox proportional hazards model (*Figure 1*), which was adjusted for age (1-year increase), sex (M vs. F), transplant eligibility (TE vs. NTE), and type of treatment (PIs vs. IMiDs vs. PIs+IMiDs).
The features with the highest impact on OS and PFS were further evaluated to build an additive score.
An inverse probability of censoring weighted (IPCW) method was used to compute the C-index estimates.[46] The discrimination ability of a model including ≥1 variables was evaluated using the C-index estimates (*Figure S1*). After the inclusion of the top 5 predictors, the 6th predictor had a significant effect on OS, but it was not significant in terms of PFS (*Figure 1*). Moreover, the C-index estimate for OS did not substantially improve with 6 compared to 5 predictors (*Figure S1*). Thus, the top 5 features with the most significant impact on OS and PFS were used to build the score.
A Cox proportional hazards model was performed in cases that were complete for all the significant prognostic features (n=2226).
A score value was assigned to each predictor and was computed as the ratio between the coefficient of the Cox model,[47] using OS as outcome (*Table 2*), and the coefficient related to the comparison ISS II vs. ISS I was used as the reference value (score value=1). The score values assigned to the predictors were calculated and rounded to the nearest 0.5. The Kaplan-Meyer curves for OS defined according to each 0.5 score point of the additive score and the grouping strategy are shown in *Figure S2*. The definition of the cut-offs used to divide the population into 4 risk-defined groups is described in the *Supplementary Appendix* and in *Table S3*.

Group differences according to the final R2-ISS classification were investigated using the Cox proportional hazards model for OS and PFS in the training and validation sets.
A log-negative log plot by R2-ISS risk group for OS was performed (*Figure S3*) as a visual approach to evaluate the proportional hazards assumption.
All reported p-values are two-sided at the conventional 5% significance level. Data were analyzed as of September 10, 2021 using R software (v3.6.3).

RESULTS

Patient characteristics and treatments

In the training set (n=7072 patients), median age was 62 years (range 18-91); 62% of patients were aged ≤65 and 38% >65 years. A total of 65% of patients were TE and 35% were NTE. During their first line of treatment, 40% of patients received an IMiD-based therapy, 15% a PI, and 46% both an IMiD and a PI. The median follow-up was 75.5 months.
In the validation set (n=3771 patients), the median age was 68 years (IQR 60-74); 42% of patients were aged ≤65 years and 58% >65 years. A total of 53% of patients were TE and 47% NTE. During their first line of treatment, 89% of patients received an IMiD-based therapy and 11% both an IMiD and a PI. The median follow-up was 60 months.

Feature selection

The individual role of each predictor was evaluated in the total population of the training set. Baseline characteristics are described in *Table 1* and the impact of each predictor on OS and PFS in *Figure 1*.
The statistically significant predictors for OS in multivariate analysis were: ISS stage (hazard ratio [HR] 2.03 [95% confidence interval 1.83-2.25] ISS III vs. I and HR 1.55 [95% CI 1.42-1.69] ISS II vs. I); del(17p) (HR 1.74 [95% CI 1.56-1.94] vs. no del(17p)); LDH >upper limit of normal ([ULN]; HR 1.66 [95% CI 1.50-1.83] vs. LDH ≤ULN); t(4;14) (HR 1.56 [95% CI 1.40-1.74] vs. no t(4;14)); 1q+ (HR 1.45 [95% CI 1.29-1.63] vs. no 1q+); t(14;16) (HR 1.34 [95% CI 1.09-1.65] vs. no t(14;16)); Eastern Cooperative Oncology Group performance status (ECOG PS) >1 (HR 1.32 [95% CI 1.20-1.44] vs. ECOG PS ≤1); IgA heavy chain (HR 1.23 [95% CI 1.14-1.34] vs. no IgA); and creatinine clearance ≤45 ml/min (HR 1.11 [95% CI 1.01-1.23] vs. creatinine clearance >45 ml/min).
The statistically significant predictors for PFS in multivariate analysis were: ISS stage (HR 1.53 [95% CI 1.42-1.66] ISS III vs. I and HR 1.35 [95% CI 1.26-1.44] ISS II vs. I); del(17p) (HR 1.41 [95% CI 1.29-1.55] vs. no del(17p)); LDH >ULN (HR 1.33 [95% CI 1.23-1.45] vs. LDH ≤ULN); t(4;14) (HR 1.49 [95% CI 1.37-1.63] vs. no t(4;14)); 1q+ (HR 1.37 [95% CI 1.25-1.50] vs. no 1q+); ECOG PS >1 (HR 1.16 [95% CI 1.08-1.25] vs. ECOG PS ≤1); IgA heavy chain (HR 1.10 [95% CI 1.03-1.17] vs. no IgA); and creatinine clearance ≤45 ml/min (HR 1.11 [95% CI 1.02-1.20] vs. creatinine clearance >45 ml/min).
Of note, t(14;16)-positive patients showed only a trend toward a shorter PFS in multivariate analysis, but it was not significant (HR 1.15 [95% CI 0.96-1.37] vs. no t(14;16), p=0.13).

Score calculation

The top predictors significantly impacting both OS and PFS (ISS, del(17p), LDH, t(4;14), and 1q+) were used to build an additive score. In the training set, data on 2226 patients were complete for all significant risk factors (*Table 1*). Four groups were identified according to the additive score: low risk (R2-ISS I, 0 points), low-intermediate risk (R2-ISS II, 0.5-1 points), intermediate-high risk (R2-ISS III, 1.5-2.5 points), high risk (R2-ISS IV, 3-5 points). The distribution of the single risk features within each R2-ISS group is shown in *Table 3*.
In the training set, R2-ISS I patients were 428 (19.2%), R2-ISS II 686 (30.8%), R2-ISS III 917 (41.2%), and R2-ISS IV 195 (8.8%). The median OS was NR (95% CI NR-NR) vs. 109.2 (95% CI

99.5-NR) vs. 68.5 (95% CI 63.9-73.9) vs. 37.9 (95% CI 32.7-46.3) months, with a 5-year OS rate of 88% (95% CI 84%-91%) vs. 75% (95% CI 71%-78%) vs. 56% (95% CI 53%-59%) vs. 37% (95% CI 31%-45%) in the R2-ISS I, II, III, and IV groups, respectively. The median PFS was 68 (95% CI 60.5-85.3) vs. 45.5 (95% CI 42.3-50.3) vs. 30.2 (95% CI 27.5-32.6) vs. 19.9 (95% CI 17.4-23.5) months, with a 5-year PFS rate of 55% (95% CI 51%-60%) vs. 40% (95% CI 36%-44%) vs. 25% (95% CI 22%-28%) vs. 17% (95% CI 12%-23%), respectively. The differences among the R2-ISS groups were statistically significant (*Figure 2a/c*).

The performance of the R2-ISS on OS in different subgroups of patients was explored. The R2-ISS maintained its discriminating ability in TE, NTE, IMiD-treated, PI-treated, and IMiD+PI-treated patients (*Figure 3*). The R2-ISS performance in terms of PFS in the same subgroups is shown in Figure S4.

In the validation set, the predictors defining the score were simultaneously present in 1214 patients (*Table 1*). R2-ISS I patients were 135 (11.1%), R2-ISS II 322 (26.5%), R2-ISS III 627 (51.6%), and R2-ISS IV 130 (10.7%). The median OS was NR (95% CI 84.7-NR) vs. 88.8 (95% CI 78.2-NR) vs. 56.2 (95% CI 50-61.9) vs. 33.9 (95% CI 27.7-40.4) months, with a 5-year OS rate of 80% (95% CI 73%-88%) vs. 70% (95% CI 64%-75%) vs. 48% (95% CI 44%-52%) vs. 24% (95% CI 17%-33%) in the R2-ISS I, II, III, and IV groups, respectively. The median PFS was 39.3 (95% CI 32.4-49.7) vs. 28 (95% CI 24.7-32.5) vs. 19.4 (95% CI 17.9-21.9) vs. 14.9 (95% CI 12.1-16.4) months, with a 5-year PFS rate of 34% (95% CI 26%-43%) vs. 26%(95% CI 21%-32%) vs. 16% (95% CI 13%-19%) vs. 10% (95% CI 6%-17%), respectively. The differences among R2-ISS groups were statistically significant (*Figure 2b/d*).

OS discrimination (*Table S4*) and OS calibration (*Figure S5*) of the R2-ISS are detailed in the *Supplementary Appendix.*

Comparison between R2-ISS and R-ISS

We were interested in identifying how many R-ISS patients were redistributed with the new R2-ISS scoring system and how R-ISS compared to R2-ISS. *Table S5* shows the redistribution of patients originally classified according to the R-ISS with the new R2-ISS risk score, and *Figure S6* shows the survival curves according to R2-ISS and R-ISS groups in the same patient population.

One of the aims of the study was to better discriminate the survival in the large group of R-ISS II patients. We therefore evaluated OS in R-ISS II patients according to the new R2-ISS score (*Figure S7*). Of note, within the R-ISS II patients in the training set, median OS was 111 months in R2-ISS II, 71 months in R2-ISS III, and 57 months in the R2-ISS IV patients**.** Within the R-ISS II patients in the validation set, median OS was 89 months in R2-ISS II, 56 months in R2-ISS III, and 27 months in the R2-ISS IV patients. These differences were statistically significant (*Figure S7a-c*), thus confirming that R-ISS II patients represent a very heterogeneous population in terms of survival that can be discriminated through the R2-ISS. The same analysis on PFS is shown in *Figure S7b/d*.

DISCUSSION

In this study, widely available prognostic tools such as ISS, LDH levels, and CA identified by FISH (del(17p), t(4;14), and 1q+) were combined to define an additive score to stratify NDMM patients. Compared with the R-ISS,[2] the R2-ISS adds 1q+ to the score, and its calculation takes into account the prognostic significance of the coexistence of several CA.

Of note, 1q+ is a very common finding in NDMM, with approximately 40% of patients presenting with this abnormality.[44] Although this variable was missing in many older trials included in this analysis, the multivariate analysis on the available patients (2770 patients in the training cohort only) clearly confirmed its prognostic role in NDMM patients.

In the analysis of CA in the validation set, a certain proportion of missing cases was also observed, although the missingness mechanism was different from that in the training set.

Indeed, CA analysis in the validation set required a centralized sample that was not mandatory, and a lower-than-expected sample compliance was registered. However, complete cases were enough to validate our score, and the OS in complete vs. incomplete cases was similar (*Figure S8*), thus revealing no evidence of selection bias.

In our analysis, t(14;16), which was included in the R-ISS, was significant in terms of OS but not of PFS and, as a consequence, was not included in the R2-ISS calculation. Indeed, despite its biological importance, t(14;16) is rare and usually presents together with other adverse prognostic factors.[48,49] Moreover, it may not be a marker of high-risk disease *per se*, as observed here and by other groups analyzing large cohorts of patients.[48,49]

Compared with the R-ISS, the R2-ISS has the advantage of being validated in an independent cohort of patients. Furthermore, a longer follow-up in this study (75.5 months vs. 46 months in the R-ISS study)[2] allowed us to analyze more precisely the OS of our patient cohort.

The additive nature of the R2-ISS score calculation allowed us to identify 4 well-separated groups of patients, rather than the 3 R-ISS categories. Of note, R2-ISS I (19.2%) plus II (30.8%) patients accounted for 50% of the entire NDMM population, while III (41.2%) plus IV (8.8%) patients for the remaining 50%. This is important because, with the R-ISS, the low- or high-risk populations were usually too small to perform subgroup analyses in trials without large numbers of patients. With the R2-ISS, the NDMM population can be split in half (I-II vs. III-IV) to develop subgroup analyses and potentially design risk-adapted approaches in a substantial number of patients.

A limitation of our study is that TE patients, especially in the training set, are more represented than NTE patients, although the R2-ISS identifies 4 separate prognostic groups in NTE patients as well. However, in the NTE population, besides disease-specific biomarkers, patient-specific biomarkers are very important[50] and the validated scores to define patient frailty should be explored in combination with the R2-ISS.[50]

The need for a long-term follow-up to develop a prognostic model impacting OS precluded us from validating R2-ISS in patients treated with new treatment combinations (e.g., carfilzomib-containing regimens,[51] triplets and quadruplets including monoclonal antibodies[52–54]). However, the validation of the R2-ISS in this patient population should be pursued as soon as the follow-up is mature enough.

The R2-ISS score was entirely developed and validated in a population of NDMM patients enrolled in clinical trials. In the future, the R2-ISS validation in a real-world population should be pursued. The applicability of the R2-ISS in clinical practice should also be tested, since complete data about all the included variables are needed to calculate the score. However, ISS (based on albumin and β2-microglobulin levels) and LDH are easily obtainable and widely available parameters, while del(17p), t(4;14), and 1q+ can be simultaneously obtained by FISH from a single bone marrow aspirate. FISH is indeed a standard procedure to be performed at MM diagnosis, and del(17p), t(4;14), and 1q+ are included in the recommended standard FISH panel.[55] As shown in the validation set, if molecular biology techniques validated against FISH are available, they can be used to calculate the R2-ISS as well.

Compared with the R-ISS, the R2-ISS has the advantage of being a flexible additive score that can be easily updated with new prognostic factors as they emerge in the MM field. Interestingly, many other factors not analyzed in this work (e.g., circulating plasma cells,[56,57] TP53 mutations,[58,59] 1p32 deletion,[60] lambda light-chain translocations,[61] extramedullary disease,[62,63] and Myc deregulation[64]) were independently associated with a dismal outcome and may potentially be included in the risk stratification strategy at baseline. Additionally, the discrimination among 1q+ cases of gain(1q) (3 copies of 1q) vs. amp(1q) (≥4 copies of 1q) may further improve the risk stratification.[58,65,66]

Moreover, molecular data (NGS[58,59] and/or GEP)[67] with a potential prognostic impact were not taken into account in the risk calculation either.

A long-term follow-up and an analysis of these prognostic factors, uniformly evaluated in a large cohort of patients, are needed to conceivably improve the current prognostic score. Moreover, we should understand whether the interaction among these risk factors could not be merely additive, but also synergistic in predicting poor prognosis.

The combination of R2-ISS and response evaluated during treatment by very sensitive techniques (e.g., minimal residual disease [MRD] inside and outside the bone marrow) should also be explored. Indeed, the achievement of MRD negativity, assessed at high sensitivity, demonstrated to overcome the poor prognosis conferred by baseline prognostic risk factors.[68] By combining R2-ISS and MRD, the design of risk-adapted plus MRD-adapted strategies can be pursued in a substantial number of NDMM patients.

As it was done for the R-ISS,[69] the value of the R2-ISS score in a population of relapsed and/or refractory MM patients should also be explored, in order to verify if this score could be used to stratify patients in trials enrolling patients after first-line treatment.

In conclusion, the R2-ISS staging system is a new simple prognostic algorithm. Compared with the R-ISS, it showed an improved discriminating capability, especially in the large group of intermediate-risk patients. The R2-ISS score includes simple and widely used prognostic markers, and the additive nature of its calculation easily allows the future inclusion of new prognostic variables.

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Tables

Table 1. Patient characteristics and treatments

Whole study population *N= 10843*		**Training set** *Total N=7072 (%)*	**Training set** *Evaluable for score calculation N=2226 (%)*	**Validation set** *Total N=3771 (%)*	**Validation set** *Evaluable for score calculation N=1214 (%)*
Age					
	Median [IQR]	62 [55-70]	60 [54-65]	68 [60-74]	68 [60.25-74]
	≤65	4397 (62)	1720 (77)	1575 (42)	495 (41)
	>65	2675 (38)	506 (23)	2196 (58)	719 (59)
Gender	Female	3216 (45)	955 (43)	1567 (42)	482 (40)
	Male	3856 (55)	1271 (57)	2204 (58)	732 (60)
ISS	Stage I	2461 (36)	830 (37)	895 (26)	276 (23)
	Stage II	2724 (40)	845 (38)	1472 (42)	554 (46)
	Stage III	1689 (25)	551 (25)	1118 (32)	384 (32)
	Missing	198	-	286	-
LDH	≤ULN	5557 (86)	1863 (84)	2017 (68)	838 (69)
	>ULN	877 (14)	363 (16)	933 (32)	376 (31)
	Missing	638	-	821	-
del(17p)	No	4990 (89)	1968 (88)	1424 (91)	1105 (91)
	Yes	633 (11)	258 (12)	135 (9)	109 (9)
	Missing	1449	-	2212	-
t(4;14)	No	4750 (87)	1949 (88)	1381 (89)	1080 (89)
	Yes	709 (13)	277 (12)	178 (11)	134 (11)
	Missing	1613	-	2212	-
1q+	No	1767 (64)	1406 (63)	1034 (66)	815 (67)
	Yes	1003 (36)	820 (37)	525 (34)	399 (33)
	Missing	4302	-	2212	-
Treatment	IMiDs	2825 (40)	506 (23)	3358 (89)	1054 (87)
	IMiDs-PIs	3221 (46)	1485 (67)	413 (11)	160 (13)
	PIs	1026 (15)	235 (11)	-	-
ASCT eligibility	NTE	2500 (35)	371 (17)	1781 (47)	575 (47)
	TE	4572 (65)	1855 (83)	1990 (53)	639 (53)

Abbreviations. N, number; IQR, interquartile range; ISS, International Staging System; LDH, lactate dehydrogenase; ULN, upper limit of normal; del, deletion; t, translocation; 1q+, 1q gain/amplification; PIs, proteasome inhibitors; IMiDs, immunomodulatory drugs, ASCT, autologous stem-cell transplantation; TE, transplant-eligible; NTE, non-transplant-eligible.

Table 2. R2-ISS score definition based on the evaluable patients included in the training set (N=2226)

Risk feature	OS HR (95% CI)	PFS HR (95% CI)	*Score value**
ISS II	1.75 (1.49 - 2.05)	1.43 (1.28 - 1.61)	*1*
ISS III	2.53 (2.13 - 3.01)	1.76 (1.54 - 2.01)	*1.5*
del(17p)	1.82 (1.53 - 2.17)	1.43 (1.23 - 1.65)	*1*
LDH high	1.60 (1.36 - 1.88)	1.37 (1.2 - 1.57)	*1*
t(4;14)	1.53 (1.29 - 1.81)	1.40 (1.21 - 1.62)	*1*
1q+	1.47 (1.29 - 1.68)	1.33 (1.2 - 1.48)	*0.5*

Group	N (%)	Total additive score
Low (I)	428 (19%)	0
Low-intermediate (II)	686 (31%)	0.5-1
Intermediate-high (III)	917 (41%)	1.5-2.5
High (IV)	195 (9%)	3-5

**Score values were calculated using OS as outcome and were rounded to the nearest 0.5. The coefficient related to the comparison ISS II vs. I was used as the reference value (score value = 1).*

Abbreviations. ISS, International Staging System; R2-ISS, Second Revision of the ISS; N, number; del, deletion; LDH, lactate dehydrogenase; t, translocation; 1q+, 1q gain/amplification; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Table 3. ISS, LDH, del(17p), t(4;14), and 1q+ distribution according to the R2-ISS in evaluable patients included in the training set (N=2226)

R2-ISS risk group	R2-ISS Low (I, N= 428)	R2-ISS Low-Int (II, N=686)	R2-ISS Int-High (III, N=917)	R2-ISS High (IV, N=195)
No risk factors	428 (100%)	-	-	-
ISS II	-	396 (58%)	407 (44%)	42 (22%)
ISS III	-	-	400 (44%)	151(77%)
LDH	-	55 (8%)	186 (20%)	122 (63%)
del(17p)	-	45 (7%)	132 (14%)	81 (42%)
t(4;14)	-	21 (3%)	159 (17%)	97(50%)
1q+	-	169 (25%)	498 (54%)	153 (78%)

Abbreviations. ISS, International Staging System; LDH, lactate dehydrogenase; del, deletion; t, translocation; 1q+, 1q gain/amplification; R2-ISS, Second Revision of the ISS; N, number; Int, intermediate.

Figure titles and legends

Figure 1. Feature selection

Panel a refers to the overall survival (OS) impact of the single variables in a multivariate Cox model; Panel b refers to the progression-free survival (PFS) impact of the single variables in a multivariate Cox model. N=7072 patients (training set).

Abbreviations. HR, hazard ratio; CI, confidence interval; *P*, p-value; ISS, International Staging System stage; NA, not available; del, deletion; LDH, lactate dehydrogenase; ULN, upper limit of normal; 1q+, 1q gain/amplification; t, translocation; ECOG PS, Eastern Cooperative Oncology Group performance status; N, number.

Figure 2. Survival outcomes in multiple myeloma patients stratified by the Second Revision of the International Staging System (R2-ISS) algorithm

Panel a refers to the overall survival (OS) in the training set; Panel b refers to the OS in the validation set; Panel c refers to the progression-free survival (PFS) in the training set; and Panel d refers to the PFS in the validation set.

Abbreviations. OS, overall survival; HR, hazard ratio; CI, confidence interval; *P*, p-value; R2-ISS, Second revision of the International Staging System stage; NR, not reached; PFS, progression-free survival.

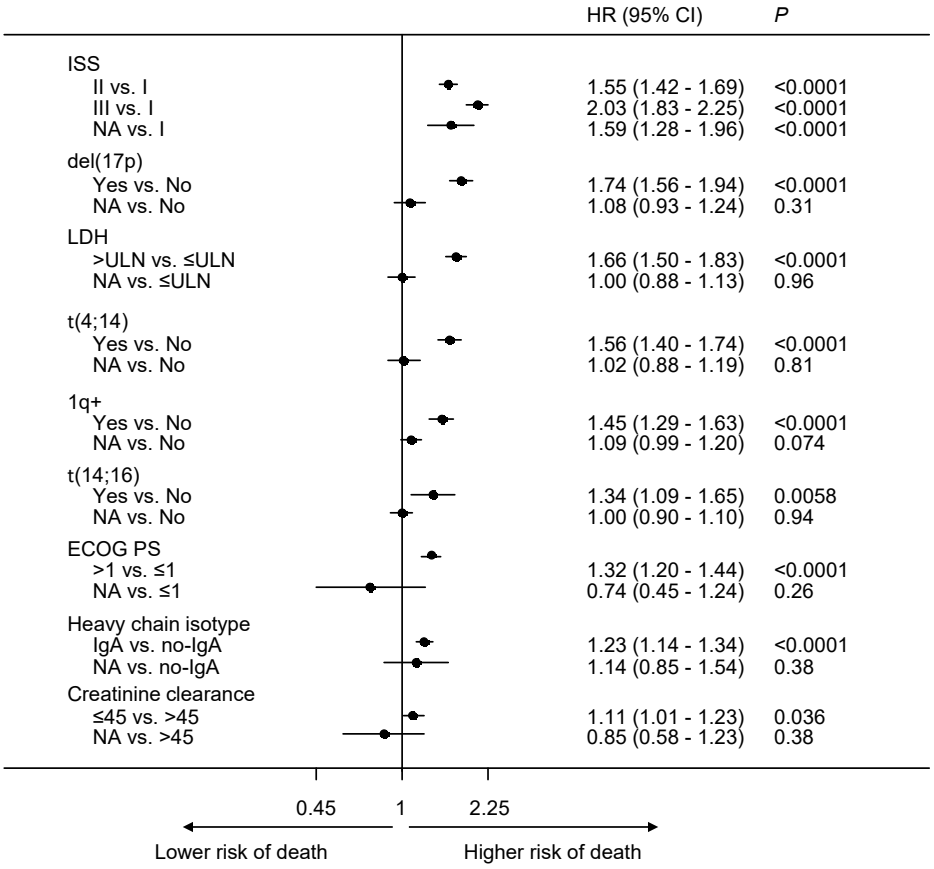
Figure 3. Second Revision of the International Staging System (R2-ISS) and overall survival by transplant eligibility and type of treatment in the training set

Panel a refers to the overall survival (OS) in transplant-eligible patients; Panel b refers to the OS in transplant-ineligible patients; Panel c refers to the OS in patients receiving regimens based on immunomodulatory drugs (IMiDs); Panel d refers to the OS in patients receiving regimens based on proteasome inhibitors (PIs); and Panel e refers to the OS in patients receiving regimens based on IMiDs plus PIs.

Abbreviations. OS, overall survival; IMiDs, immunomodulatory drugs; PIs, proteasome inhibitors; HR, hazard ratio; CI, confidence interval; *P*, p-value; R2-ISS, Second revision of the International Staging System stage; NR, not reached.

Figure 1

1a. OS



1b. PFS

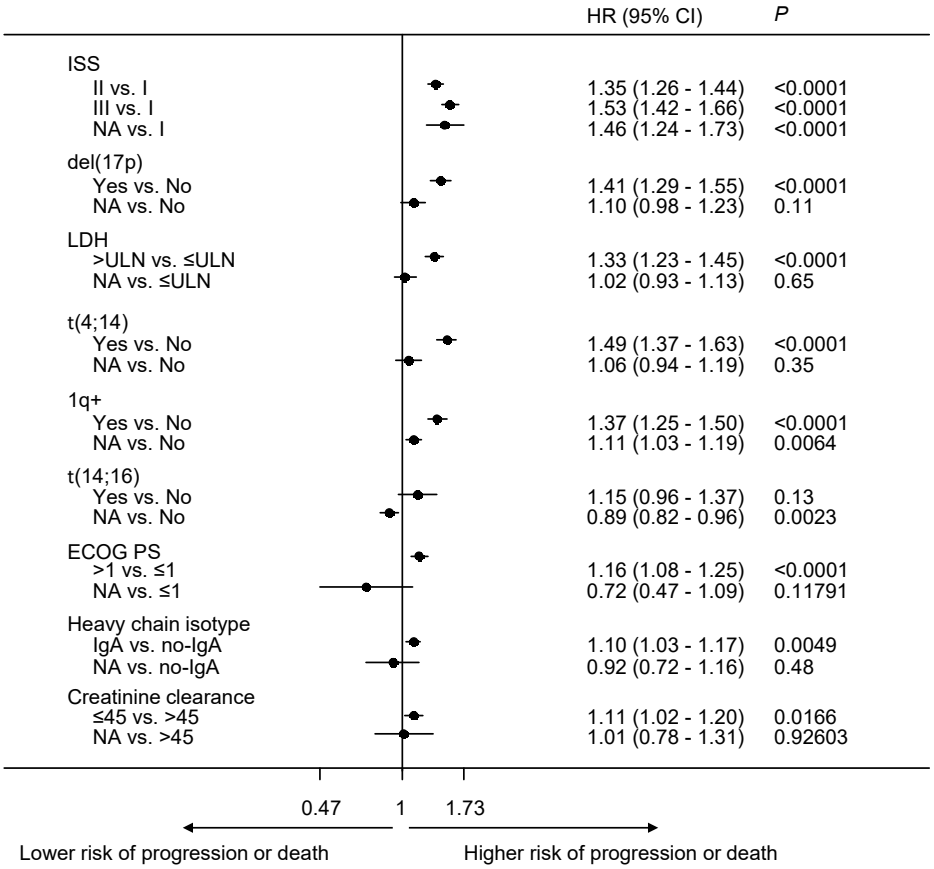


Figure 2

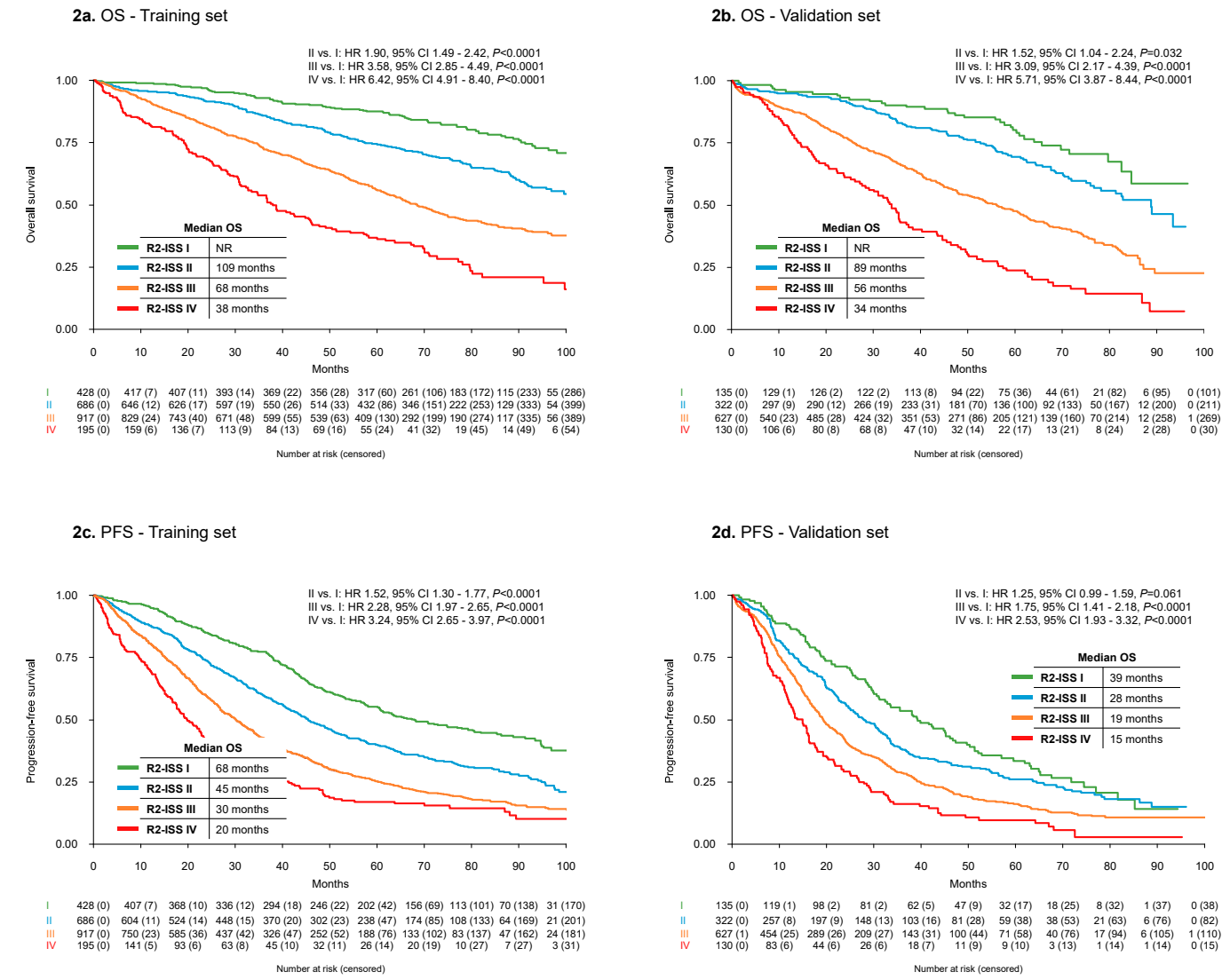
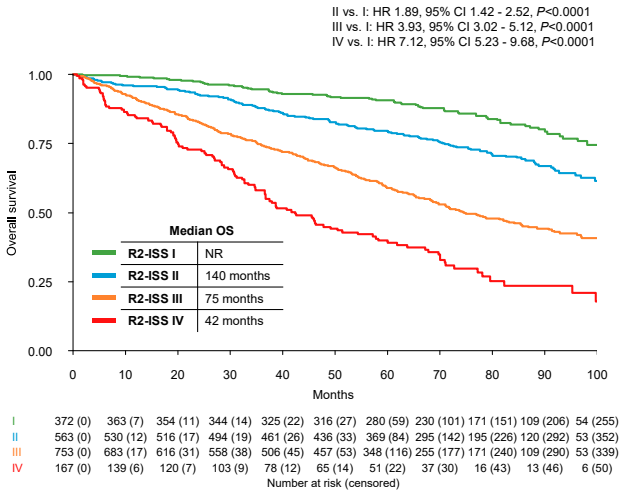
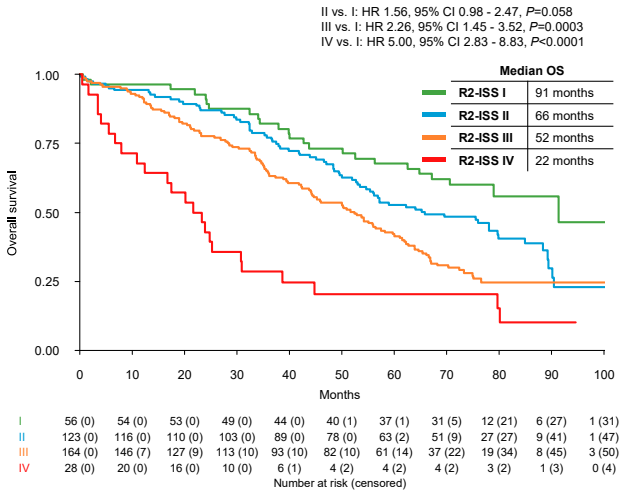

2a. OS - Training set
II vs. I: HR 1.90, 95% CI 1.49 - 2.42, P<0.0001
III vs. I: HR 3.58, 95% CI 2.85 - 4.49, P<0.0001
IV vs. I: HR 6.42, 95% CI 4.91 - 8.40, P<0.0001
Overall survival
Median OS
R2-ISS I NR
R2-ISS II 109 months
R2-ISS III 68 months
R2-ISS IV 38 months
Months
I 428 (0) 417 (7) 407 (11) 393 (14) 369 (22) 356 (28) 317 (60) 261 (106) 183 (172) 115 (233) 55 (286)
II 686 (0) 646 (12) 626 (17) 597 (19) 550 (26) 514 (33) 432 (86) 346 (151) 222 (253) 129 (333) 54 (399)
III 917 (0) 829 (24) 743 (40) 671 (48) 599 (55) 539 (63) 409 (130) 292 (199) 190 (274) 117 (335) 56 (389)
IV 195 (0) 159 (6) 136 (7) 113 (9) 84 (13) 69 (16) 55 (24) 41 (32) 19 (45) 14 (49) 6 (54)
Number at risk (censored)
2b. OS - Validation set
II vs. I: HR 1.52, 95% CI 1.04 - 2.24, P=0.032
III vs. I: HR 3.09, 95% CI 2.17 - 4.39, P<0.0001
IV vs. I: HR 5.71, 95% CI 3.87 - 8.44, P<0.0001
Overall survival
Median OS
R2-ISS I NR
R2-ISS II 89 months
R2-ISS III 56 months
R2-ISS IV 34 months
Months
I 135 (0) 129 (1) 126 (2) 122 (2) 113 (8) 94 (22) 75 (36) 44 (61) 21 (82) 6 (95) 0 (101)
II 322 (0) 297 (9) 290 (12) 266 (19) 233 (31) 181 (70) 136 (100) 92 (133) 50 (167) 12 (200) 0 (211)
III 627 (0) 540 (23) 485 (28) 424 (32) 351 (53) 271 (86) 205 (121) 139 (160) 70 (214) 12 (258) 1 (269)
IV 130 (0) 106 (6) 80 (8) 68 (8) 47 (10) 32 (14) 22 (17) 13 (21) 8 (24) 2 (28) 0 (30)
Number at risk (censored)
2c. PFS - Training set
II vs. I: HR 1.52, 95% CI 1.30 - 1.77, P<0.0001
III vs. I: HR 2.28, 95% CI 1.97 - 2.65, P<0.0001
IV vs. I: HR 3.24, 95% CI 2.65 - 3.97, P<0.0001
Progression-free survival
Median OS
R2-ISS I 68 months
R2-ISS II 45 months
R2-ISS III 30 months
R2-ISS IV 20 months
Months
I 428 (0) 407 (7) 368 (10) 336 (12) 294 (18) 246 (22) 202 (42) 156 (69) 113 (101) 70 (138) 31 (170)
II 686 (0) 604 (11) 524 (14) 448 (15) 370 (20) 302 (23) 238 (47) 174 (85) 108 (133) 64 (169) 21 (201)
III 917 (0) 750 (23) 585 (36) 437 (42) 326 (47) 252 (52) 188 (76) 133 (102) 83 (137) 47 (162) 24 (181)
IV 195 (0) 141 (5) 93 (6) 63 (8) 45 (10) 32 (11) 26 (14) 20 (19) 10 (27) 7 (27) 3 (31)
Number at risk (censored)
2d. PFS - Validation set
II vs. I: HR 1.25, 95% CI 0.99 - 1.59, P=0.061
III vs. I: HR 1.75, 95% CI 1.41 - 2.18, P<0.0001
IV vs. I: HR 2.53, 95% CI 1.93 - 3.32, P<0.0001
Progression-free survival
Median OS
R2-ISS I 39 months
R2-ISS II 28 months
R2-ISS III 19 months
R2-ISS IV 15 months
Months
I 135 (0) 119 (1) 98 (2) 81 (2) 62 (5) 47 (9) 32 (17) 18 (25) 8 (32) 1 (37) 0 (38)
II 322 (0) 257 (8) 197 (9) 148 (13) 103 (16) 81 (28) 59 (38) 38 (53) 21 (63) 6 (76) 0 (82)
III 627 (1) 454 (25) 289 (26) 209 (27) 143 (31) 100 (44) 71 (58) 40 (76) 17 (94) 6 (105) 1 (110)
IV 130 (0) 83 (6) 44 (6) 26 (6) 18 (7) 11 (9) 9 (10) 3 (13) 1 (14) 1 (14) 0 (15)
Number at risk (censored)

Figure 3

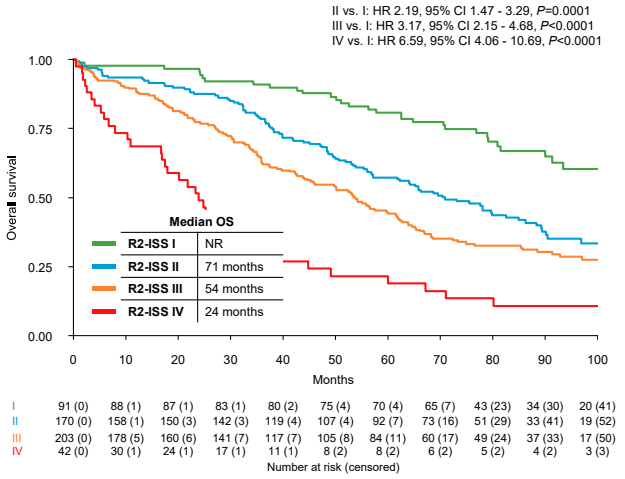
3a. OS in transplant-eligible patients



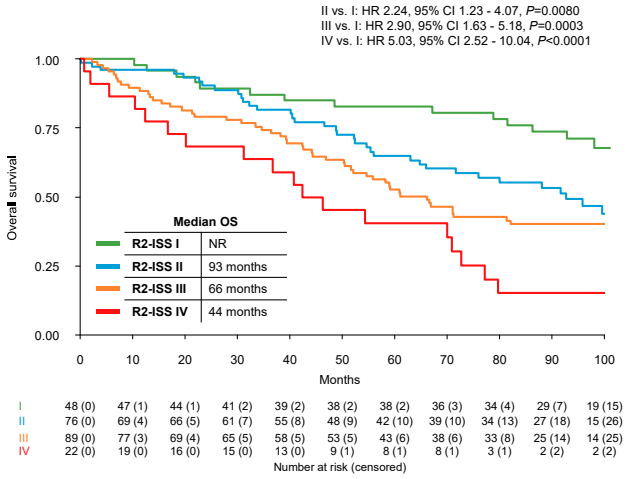
3b. OS in transplant-ineligible patients



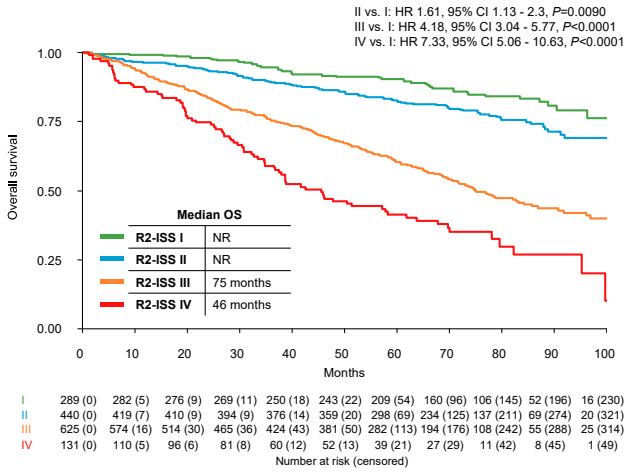
3c. OS in patients receiving IMiD-based regimens



3d. OS in patients receiving PI-based regimens



3e. OS in patients receiving IMiD plus PI-based regimens



Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project

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Supplementary methods and results

HARMONY data quality gate

The minimal essential data to be registered in the HARMONY platform were unique patient record identifier, diagnosis date, year of birth, protocol code, randomization arm, gender, transplant eligibility, death occurrence, treatment discontinuation, date of the last follow-up, time-to-progression (TTP) event, TTP date, TTP in months, progression-free survival (PFS) event, PFS date, PFS in months, overall survival (OS) event, OS date, and OS in months.
Patients who had incomplete data about the above-mentioned variables were not included in the HARMONY Platform and, consequently, were not included in this analysis.

Features included in the analyses

The stages of the International Staging System (ISS I, II, III) were defined as described in the main manuscript (see the *Patients* section), according to serum β2-microglobulin and albumin levels.[1]
Serum levels of lactate dehydrogenase (LDH) were measured at baseline. The upper limit of normal (ULN) ranges were defined by the local laboratories. High LDH was defined as >ULN; Normal LDH as ≤ULN.
The stages of the Revised ISS (R-ISS I, II, III) were defined as previously described, according to ISS stage, high-risk CA [defined as the presence of at least one among del(17p) deletion, t(4;14)(p16;q32) translocation, and/or t(14;16)(q32;q23) translocation], and LDH levels.[2]
The Eastern Cooperative Oncology Group performance status (ECOG PS) was assessed by the treating physician at the diagnosis of multiple myeloma (MM).
The heavy chain isotype of myeloma-specific monoclonal protein was evaluated at baseline through immune fixation.
Creatinine clearance was calculated according to the Modification of Diet in Renal Disease (MDRD) formula.[3]
The following risk factors were compared: ISS stage (II vs. I, III vs. I, not available [NA] vs. I); LDH (>upper limit of normal [ULN] vs. ≤ULN, NA vs. ≤ULN); del(17p) (Yes vs. No, NA vs. No); t(4;14) (Yes vs. No, NA vs. No); 1q gain/amplification ([1q+], Yes vs. No, NA vs. No); t(14;16) (Yes vs. No, NA vs. No); Eastern Cooperative Oncology Group performance status ([ECOG PS], >1 vs. ≤1, NA vs. ≤1);[4] heavy chain isotype (IgA vs. non-IgA, NA vs. non-IgA);[5] and creatinine clearance (≤45 vs. >45 ml/min, NA vs. >45 ml/min).[6]

Chromosomal abnormalities

Analyses were performed by interphase fluorescence in situ hybridization (FISH) in few European laboratories. Despite the inter-laboratory variability, all analyses were performed on purified plasma cells obtained with immunomagnetic techniques, and the analyses of del(17p), t(4;14), 1q+, and t(14;16) were commonly included in each multiple myeloma (MM) panel and tested using commercial probes. Of note, although the cut-off levels were not identical, they were very similar, ranging from 10% to 20% for numerical aberrations and from 10% to 15% for IgH translocations.
Translocations and copy-number alterations in the NCRI Myeloma XI trial were centrally analyzed by real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) and multiplex ligation-dependent probe amplification (MLPA, a technique validated against FISH), as previously described.[7]

Grouping strategy

In the Second Revision of the International Staging System (R2-ISS) score, in order to identify 4 risk-defined groups, we defined the cut-offs according to the highest possible C-index

estimate by using the inverse probability of censoring weighted (IPCW) method with the following constraints: 1) each group must be represented by at least 5% of the total population and (2) the 5-year survival probability of the highest-risk group must be less than 40% (representing the 5-year survival probability of R-ISS III patients).[2] The cut-offs with the best performances are shown in *Table S3*, while the final grouping strategy is shown in *Table 2* and *Figure S2*.

Proportional hazards assessment

A log-negative log plot by R2-ISS risk group for OS was performed in the training (*Figure S3a*) and validation (*Figure S3b*) sets as a visual approach to evaluate the proportional hazards assumption.

OS calibration of the R2-ISS

In order to test the OS calibration of the R2-ISS, we focused on transplant-eligible patients receiving a treatment based on an immunomodulatory drug (IMiD). This population was well represented and similarly treated both in the training (n=234) and validation (n=547) sets.
Of note, patients belonging to the same R2-ISS risk group did not show significant differences in the training vs. validation sets, and the median OS and 5-year OS rates were very similar (*Figure S5*).

Inverse probability of censoring weighted (IPCW) method to estimate the C-index for OS according to the R2-ISS and R-ISS

In order to test the OS discrimination in the training and validation cohorts of the R2-ISS and to compare it with that of the R-ISS, we computed the C-index estimates at different time points according to the IPCW method (*Table S4*). We used the IPCW method in order to avoid bias due to the underlying censoring distribution. A Cox censoring model was used for the IPCW method. Ties in the discrete predictors were removed in order to avoid bias due to a comparison between a four-category classifier (R2-ISS) and a three-category classifier (R-ISS).
The R2-ISS showed similar C-index estimates in the training and validation cohorts.
The R2-ISS and R-ISS showed similar C-index estimates (slightly higher C-index estimates for the R-ISS in the training set and slightly higher C-index estimates for the R2-ISS in the validation set). In conclusion, the R2-ISS was able to discriminate OS in both cohorts, and its main advantage over the R-ISS was not a clear C-index estimate advantage, but a better distribution of the intermediate-risk patients.

Supplementary tables

Table S1. Patient demographics in the sixteen studies included in the analysis

		All N=10843 (%)	*EMN01* N=654 (%)	*EMN02/HO95 MM* N=1493 (%)	*GEM05MAS65* N=259 (%)	*GEM05MENOS65* N=389 (%)	*GEM2010MAS65* N=236 (%)	*GIMEMA-MM-03-05* N=511 (%)	*HOVON-65/ GMMG-HD4* N=826 (%)	*HOVON-87/ NMSG-18* N=630 (%)	*IST-CAR-506* N=58 (%)	*MM-BO2005* N=474 (%)	*GMMG-MM5* N=502 (%)	*26866138 MMY2069* N=152 (%)	*RV-MM-EMN-441* N=387 (%)	*RV-MM-PI-114* N=102 (%)	*RV-MM-PI-209* N=399 (%)	*NCRI Myeloma XI** N=3771 (%)
Gender	**F**	4783 (44)	335 (51)	630 (42)	124 (48)	212 (54)	112 (47)	259 (51)	327 (40)	288 (46)	31 (53)	201 (42)	202 (40)	74 (49)	192 (50)	49 (48)	180 (45)	1567 (42)
	M	6060 (56)	319 (49)	863 (58)	135 (52)	177 (46)	124 (53)	252 (49)	499 (60)	342 (54)	27 (47)	273 (58)	300 (60)	78 (51)	195 (50)	53 (52)	219 (55)	2204 (58)
ISS	**I**	3356 (32)	181 (28)	579 (39)	63 (24)	150 (39)	53 (23)	115 (28)	287 (38)	159 (26)	16 (28)	215 (45)	193 (38)	41 (27)	170 (44)	48 (53)	191 (48)	895 (26)
	II	4196 (41)	296 (45)	584 (39)	109 (42)	159 (41)	106 (46)	187 (46)	280 (37)	301 (48)	19 (33)	182 (38)	162 (32)	44 (29)	151 (39)	30 (33)	114 (29)	1472 (42)
	III	2807 (27)	177 (27)	330 (22)	87 (34)	80 (21)	73 (31)	105 (26)	188 (25)	163 (26)	23 (40)	77 (16)	147 (29)	67 (44)	66 (17)	12 (13)	94 (24)	1118 (32)
	Missing	484	0	0	0	0	4	104	71	7	0	0	0	0	0	12	0	286
LDH	**≤ULN**	7574 (81)	473 (89)	1183 (85)	230 (89)	327 (84)	205 (89)	373 (88)	652 (82)	479 (90)	35 (88)	385 (90)	384 (77)	82 (83)	310 (93)	78 (91)	361 (90)	2017 (68)
	>ULN	1810 (19)	56 (11)	210 (15)	29 (11)	62 (16)	25 (11)	51 (12)	142 (18)	51 (10)	5 (12)	43 (10)	116 (23)	17 (17)	24 (7)	8 (9)	38 (10)	933 (32)
	Missing	1459	125	100	0	0	6	87	32	100	18	46	2	53	53	16	0	821
del(17p)	**No**	6414 (89)	460 (86)	1102 (89)	207 (90)	307 (94)	155 (91)	321 (85)	536 (89)	389 (90)	43 (84)	409 (93)	412 (89)	109 (85)	236 (89)	66 (85)	238 (85)	1424 (91)
	Yes	768 (11)	76 (14)	140 (11)	24 (10)	19 (6)	15 (9)	55 (15)	65 (11)	43 (10)	8 (16)	33 (7)	53 (11)	19 (15)	29 (11)	12 (15)	42 (15)	135 (9)
	Missing	3661	118	251	28	63	66	135	225	198	7	32	37	24	122	24	119	2212
t(4;14)	**No**	6131 (87)	471 (89)	1055 (88)	210 (91)	288 (87)	93 (81)	317 (84)	441 (86)	423 (91)	42 (82)	354 (80)	412 (89)	119 (93)	215 (84)	63 (80)	247 (85)	1381 (89)
	Yes	887 (13)	59 (11)	143 (12)	20 (9)	43 (13)	22 (19)	59 (16)	70 (14)	40 (9)	9 (18)	87 (20)	49 (11)	9 (7)	41 (16)	16 (20)	42 (15)	178 (11)
	Missing	3825	124	295	29	58	121	135	315	167	7	33	41	24	131	23	110	2212
1q+	**No**	2801 (65)	9 (56)	731 (62)	0	0	0	73 (55)	430 (73)	223 (63)	0	0	269 (60)	0	9 (56)	9 (45)	14 (78)	1034 (66)
	Yes	1528 (35)	7 (44)	440 (38)	0	0	0	59 (45)	163 (27)	131 (37)	0	0	181 (40)	0	7 (44)	11 (55)	4 (22)	525 (34)
	Missing	6514	638	322	259	389	236	379	233	276	58	474	52	152	371	82	381	2212
Treatment	**IMiDs**	6183 (57)	654 (100)			103 (26)			414 (50)	630 (100)		238 (50)			387 (100)		399 (100)	3358 (89)
	IMiDs plus PIs	3634 (34)		1493 (100)	176 (68)	222 (57)	236 (100)	254 (50)				236 (50)	502 (100)			102 (100)		413 (11)
	PIs	1026 (9)			83 (32)	64 (16)		257 (50)	412 (50)		58 (100)			152 (100)				

		All N=10843 (%)	*EMN01* N=654 (%)	*EMN02/HO95 MM* N=1493 (%)	*GEM05MAS65* N=259 (%)	*GEM05MENOS65* N=389 (%)	*GEM2010MAS65* N=236 (%)	*GIMEMA-MM-03-05* N=511 (%)	*HOVON-65/GMMG-HD4* N=826 (%)	*HOVON-87/NMSG-18* N=630 (%)	*IST-CAR-506* N=58 (%)	*MM-BO2005* N=474 (%)	*GMMG-MM5* N=502 (%)	*26866138 MMY2069* N=152 (%)	*RV-MM-EMN-441* N=387 (%)	*RV-MM-PI-114* N=102 (%)	*RV-MM-PI-209* N=399 (%)	*NCRI Myeloma XI** N=3771 (%)
ASCT eligibility	**NTE**	4281 (39)	654 (100)		259 (100)		236 (100)	511 (100)		630 (100)	58 (100)			152 (100)				1781 (47)
	TE	6562 (61)		1493 (100)		389 (100)			826 (100)			474 (100)	502 (100)		387 (100)	102 (100)	399 (100)	1990 (53)
Evaluable to calculate R2-ISS	**No**	7403 (68)	643 (98)	524 (35)	259 (100)	389 (100)	236 (100)	412 (81)	431 (52)	369 (59)	58 (100)	474 (100)	60 (12)	152 (100)	372 (96)	86 (84)	381 (95)	2557 (68)
	Yes	3440 (32)	11 (2)	969 (65)				99 (19)	395 (48)	261 (41)			442 (88)		15 (4)	16 (16)	18 (5)	1214 (32)
R2-ISS	**I**	563 (16)	1 (9)	197 (20)				13 (13)	82 (21)	42 (16)			82 (19)		4 (27)	2 (12)	5 (28)	135 (11)
	II	1008 (29)	2 (18)	302 (31)				24 (24)	122 (31)	97 (37)			119 (27)		7 (47)	5 (31)	8 (44)	322 (27)
	III	1544 (45)	7 (64)	392 (40)				52 (53)	149 (38)	105 (40)			195 (44)		4 (27)	8 (50)	5 (28)	627 (52)
	IV	325 (9)	1 (9)	78 (8)				10 (10)	42 (11)	17 (7)			46 (10)		0 (0)	1 (6)	0 (0)	130 (11)
	Missing	7403	643	524	259	389	236	412	431	369	58	474	60	152	372	86	381	2557

Patients not passing the HARMONY data quality gate were excluded from the analysis.

**518 patients receiving KCRd (carfilzomib, cyclophosphamide, lenalidomide, and dexamethasone) were not included because overall survival data were not available in the platform.*

Abbreviations. N, number; F, female; M, male; ISS, International Staging System stage, LDH, lactate dehydrogenase; ULN, upper limit of normal; del, deletion; t, translocation; 1q+, 1q gain/amplification; IMiDs, immunomodulatory drugs; PIs, proteasome inhibitors; ASCT, autologous stem-cell transplantation; TE, transplant-eligible patients; NTE, non-transplant-eligible patients; R2-ISS, Second Revision of the ISS stage.

Table S2. Treatment regimens in the source studies

Trial	Regimens and doses	N *(only randomized patients are shown)*	Age, median, years (IQR)
EMN01[8,9] ClinicalTrials.gov ID NCT01093196	ARM A R: lenalidomide os 25 mg/die for 21 days D: dexamethasone os 40 mg d 1, 8, 15, 22 or 20 mg in patients aged >75 years	217	73 (70-77)
	ARM B M: melphalan os 0.18 mg/Kg or 0.13 mg/Kg in patients aged >75 years d 1–4 P: prednisone os 1.5 mg/Kg d1–4 R: lenalidomide os 10 mg/die for 21 days	217	
	ARM C C: cyclophosphamide os 50 mg/die for 21 days or 50 mg every other day in patients aged >75 years P: prednisone os 25 mg every other day R: lenalidomide os 25 mg/d for 21 days (nine 28-day cycles followed by maintenance treatment with lenalidomide or lenalidomide and prednisone)	220	
EMN02/HO95[10,11] **(HOVON 95 MM)** ClinicalTrials.gov ID NCT01208766	4 bortezomib-cyclophosphamide-dexamethasone induction cycles ARM A V: bortezomib iv (sc after protocol amendment) 1.3 mg/mq d 1, 4, 8, 11, 22, 25, 29, 32 M: melphalan os 9mg/m^2 d 1–4 P: prednisone os 60 mg/m^2 d 1–4 (four 6-week cycles followed by bortezomib-lenalidomide-dexamethasone consolidation and lenalidomide maintenance or no consolidation and lenalidomide maintenance)	495	58 (52-62)
	ARM B 1 or 2 cycles of melphalan iv 200 mg/m^2 followed by stem-cell support (followed by bortezomib-lenalidomide-dexamethasone consolidation and lenalidomide maintenance or no consolidation and lenalidomide maintenance)	702	

GEM05MAS65[12–14] ClinicalTrials.gov ID NCT00443235	ARM A V: bortezomib iv 1.3 mg/m^2 d 1, 4, 8, 11, 22, 25, 29, 32 of cycle 1 followed by iv bortezomib (1.3 mg/m^2) d 1, 8, 15, 22 M: melphalan os 9mg/m^2 d 1–4 P: prednisone os 60 mg/m^2 d 1–4 (one 6-week cycle and five 5-week cycles followed by maintenance treatment with bortezomib-thalidomide or bortezomib-prednisone) ARM B V: bortezomib iv 1.3 mg/m^2 d 1, 4, 8, 11, 22, 25, 29, 32 of cycle 1 followed by iv bortezomib (1.3 mg/m^2) d 1, 8, 15, 22 T: thalidomide os 100 mg daily P: prednisone os 60 mg/m^2 d 1–4 (one 6-week cycle and five 5-week cycles followed by maintenance treatment with bortezomib-thalidomide or bortezomib-prednisone)	130 130	73 (69-76)
GEM05MENOS65[15,16] ClinicalTrials.gov ID NCT00461747	ARM A V: vincristine iv 0.03 mg/kg (upper limit, 2 mg) d 1 B: BCNU 0.5 mg/kg iv d 1 M: melphalan 0.25 mg/kg os d 1–4 C: cyclophosphamide 10 mg/Kg iv d 1 P: prednisone 1 mg/kg d 1–4, 0.5 mg/kg d 5–8, and 0.25 mg/kg d 9–12 V: vincristine 1 mg iv d 1 B: BCNU 30 mg/m^2 iv d 1 A: doxorubicin 40 mg/m^2 iv d 1 D: dexamethasone 40 mg per os d 1–4, 9–12, 17–20. (four 35-day alternating cycles, followed by two bortezomib cycles d 1, 4, 8, 11, followed by 1 or 2 cycles of melphalan 200 mg/m^2 and stem-cell support) ARM B T: thalidomide os 200 mg daily (with escalating doses from 50 mg to 100 mg to 200 mg) D: dexamethasone os 40 mg d 1–4, and 9–12 (six 4-week cycles, followed by 1 or 2 cycles of melphalan 200 mg/m^2 and stem-cell support) ARM C V: bortezomib iv 1.3 mg/m^2 d 1, 4, 8, 11 T: thalidomide os 200 mg daily (with escalating doses from 50 mg to 100 mg to 200 mg) D: dexamethasone os 40 mg d 1–4, 9–12 (six 4-week cycles, followed by 1 or 2 cycles of melphalan 200 mg/m^2 and stem-cell support)	129 127 130	57 (51-61)

GEM2010MAS65[17] ClinicalTrials.gov ID NCT01237249	ARM A (sequential) V: bortezomib iv 1.3 mg/m^2 d 1, 4, 8, 11, 22, 25, 29, 32 of cycle 1, followed by iv bortezomib (1.3 mg/m^2) d 1, 8, 15, 22 M: melphalan os 9 mg/m^2 d 1–4 P: prednisone os 60 mg/m^2 d 1–4 (one 6-week cycle and eight 4-week cycles) R: lenalidomide 25 d 1–21 d: Dexamethasone 40 mg d 1, 8, 15, 22 (nine 4-week cycles) ARM B (alternating) V: bortezomib iv 1.3 mg/m^2 d 1, 4, 8, 11, 22, 25, 29, 32 of cycle 1 followed by iv bortezomib (1.3 mg/m^2) d 1, 8, 15, 22 M: melphalan os 9mg/m^2 d 1–4 P: prednisone os 60 mg/m^2 d 1–4 (one 6-week cycle and eight 4-week cycles) R: lenalidomide 25 d 1–21 d: Dexamethasone 40 mg d 1, 8, 15, 22 (nine 4-week cycles)	118 115	74 (70-78)
GIMEMA-MM-03-05[18,19] ClinicalTrials.gov ID NCT01063179	ARM A V: bortezomib iv 1.3 mg d 1, 8, 15, 22 M: melphalan os 9 mg/m^2 d 1–4 or 2 mg every other day P: prednisone os 60 mg/m^2 d 1–4 ARM B V: bortezomib iv 1.3 mg/m^2 d 1, 8, 15, 22 M: melphalan os 9 mg/m^2 d 1–4 P: prednisone os 60 mg/m^2 d 1–4 T: thalidomide os 50 mg (only in the VMPT arm: nine 28-day cycles followed by maintenance treatment with bortezomib and thalidomide until PD)	257 254	71 (69-75.5)

HOVON-65/GMMG-HD4[20,21] EudraCT No. 2004-000944-26	ARM A V: vincristine iv 0.4 mg d 1–4 A: doxorubicin iv 9 mg/m^2 d 1–4 D: dexamethasone os 50 mg d 1–4, 9–12, 17–20 (three 28-day cycles, followed by 1 or 2 cycles of melphalan 200 mg/m^2 and stem-cell support, followed by maintenance treatment with thalidomide 50 mg per day for 2 years) ARM B P: bortezomib iv 1.3 mg d 1, 4, 8, 11 A: doxorubicin iv 9 mg/m^2 d 1–4 D: dexamethasone os 50 mg d 1–4, 9–12, 17–20 (three 28-day cycles, followed by 1 or 2 cycles of melphalan 200 mg/m^2 and stem-cell support, followed by maintenance treatment with iv bortezomib 1.3 mg/m^2 once every 2 weeks for 2 years)	414 412	57 (51-61)
HOVON-87/NMSG-18[22] EudraCT No. 2007-004007-34	ARM A M: melphalan os 0.18 mg/Kg d 1–4 P: prednisone os 2 mg/Kg d 1–4 T: thalidomide 200 m daily (nine 4-week cycles followed by thalidomide maintenance) ARM B M: melphalan os 0.18mg/Kg d 1–4 P: prednisone os 2 mg/Kg d 1–4 R: lenalidomide 25 mg d 1–21 (nine 4-week cycles followed by lenalidomide maintenance)	318 319	73 (70-77.8)
IST-CAR-506[23] ClinicalTrials.gov ID NCT01346787	C: carfilzomib iv 20 mg/m^2 d 1, 2 of cycle 1, followed by 36 mg/m^2 d 8, 9, 15, 16 of all subsequent cycles C: cyclophosphamide os 300 mg/m^2 d 1, 8, 15 D: dexamethasone os 40 mg d 1, 8, 15, 22 (nine 28-day cycles followed by maintenance treatment with carfilzomib alone until PD)	58	71 (68-75.8)

MM-BO2005[24,25] ClinicalTrials.gov ID NCT01134484	ARM A V: bortezomib iv 1.3 mg d 1, 4, 8, 11 T: thalidomide os 100 mg daily for the first 14 days and 200 mg daily thereafter D: dexamethasone os 40 mg d 1, 2, 4, 5, 8, 9, 11, 12 (three 21-day cycles, followed by 2 cycles of melphalan iv 200 mg/m^2 and stem-cell support, followed by consolidation with 2 VTD cycles) ARM B T: thalidomide os 100 mg daily for the first 14 days and 200 mg daily thereafter D: dexamethasone os 40 mg d 1, 2, 4, 5, 8, 9, 11, 12 (three 21-day cycles, followed by 2 cycles of melphalan 200 mg/m^2 and stem-cell support, followed by consolidation with 2 TD cycles)	236 238	57 (52-62)
GMMG-MM5[26,27] EudraCT No. 2010-019173-16	ARM A1 + B1 P: bortezomib 1.3 mg/m^2 d 1, 4, 8, 11 A: doxorubicin iv 9 mg/m^2 d 1–4 D: dexamethasone os 20 mg d 1–4, 9–12, 17–20 (three 4-week cycles followed by single MEL200-ASCT or tandem MEL200-ASCT in patients with a response less than near CR, followed by lenalidomide consolidation and lenalidomide maintenance until progression or for 2 years [arms A1+A2] or until achievement of CR [arms B1+B2]) ARM A2 + B2 V: bortezomib 1.3 mg/m^2 d 1, 4, 8, 11 C: cyclophosphamide 900 mg/m^2 iv d 1 D: dexamethasone os 40 mg d 1–2, 4–5, 8–9, 11–12 (three 3-week cycles followed by single MEL200-ASCT or tandem MEL200-ASCT in patients with a response less than near CR, followed by lenalidomide consolidation and lenalidomide maintenance until progression or for 2 years [arms A1+A2] or until achievement of CR [arms B1+B2])	251 251	59 (52.3-64)

26866138MMY2069[28] ClinicalTrials.gov ID NCT01190787	GROUP 1 V: bortezomib sc 1.3 mg/m^2 d 1, 8, 15, 22 P: prednisone os 50 mg every other day GROUP 2 C: cyclophosphamide os 50 mg every other day V: bortezomib sc 1.3 mg/m^2 d 1, 8, 15, 22 P: prednisone os 50 mg every other day GROUP 3 V: bortezomib sc 1.3 mg d 1, 8, 15, 22 M: melphalan os 2 mg every other day P: prednisone os 50 mg every other day (nine 28-day cycles followed by maintenance treatment with bortezomib until PD)	51 51 50	77 (74.8-80)
RV-MM-EMN-441[29] ClinicalTrials.gov ID NCT01091831	4 lenalidomide-dexamethasone induction cycles ARM A C: cyclophosphamide os 300 mg/m^2 d 1, 8, 15 R: lenalidomide os 25 mg/d for 21 days D: dexamethasone os 40 mg d 1, 8, 15, 22 (six 28-day cycles followed by maintenance treatment with lenalidomide or lenalidomide and prednisone) ARM B 2 cycles of melphalan iv 200 mg/m^2 followed by stem-cell support (followed by maintenance treatment with lenalidomide or lenalidomide and prednisone)	129 127	57 (53-62)
RV-MM-PI-114[30,31] EudraCT No. 2005-004730-41	P: bortezomib iv 1.3 mg, d 1, 4, 8, 11 A: pegylated liposomal doxorubicin iv 30 mg/m^2 d 4 D: dexamethasone d 1–4, 8–11, 15–18 of cycle 1 and d 1–4 of cycles 2 to 4 2 cycles of melphalan iv 100 mg/m^2 followed by consolidation with lenalidomide 25 mg/d for 21 days + prednisone 50 mg every other day followed by maintenance treatment with lenalidomide 10 mg/d for 21 days until PD	102	67 (63-70)

MM-RV-PI-209[32] ClinicalTrials.gov ID NCT00551928	4 lenalidomide-dexamethasone induction cycles ARM A M: melphalan os 0.18 mg/Kg d 1–4 P: prednisone os 2 mg/Kg d 1–4 R: lenalidomide os 10 mg/d for 21 days (six 28-day cycles followed by maintenance treatment with lenalidomide or no maintenance) ARM B 2 cycles of melphalan iv 200 mg/m^2 followed by stem-cell support (followed by maintenance treatment with lenalidomide or no maintenance)	132 141	58 (52-61)
NCRI MYELOMA XI[33–37] ISRCTN Registry No. ISRCTN49407852 Clinicaltrialsregister.eu No. 2009-010956-93 Primary Funder Cancer Research UK [C1298/A10410] [C7852/A25447]	INTENSIVE TREATMENT PATHWAY CTD: 21-day cycles of cyclophosphamide (C) 500 mg os d 1, 8, 15; thalidomide (T) 100 mg (increasing to 200 mg as tolerated) os daily; and dexamethasone (D) 40 mg os d 1–4, 12–15 CRD: 28-day cycles of cyclophosphamide (C) 500 mg os d 1, 8; lenalidomide (R) 25 mg os d 1–21; and dexamethasone (D) 40 mg os d 1–4, 12–15 KCRD: 28-day cycles of carfilzomib (K) 36mg/m^2 iv d 1–2, 8–9, 15–16; cyclophosphamide (C) 500mg os d 1, 8, lenalidomide (R) 25mg os d 1-21; and dexamethasone (D) 40mg os d 1–4, 8–9, 15–16 Initial induction treatment was administered in the absence of toxicity, consent withdrawal, or progression, for a minimum of 4 cycles and until maximum response followed by high-dose melphalan + ASCT. NON-INTENSIVE TREATMENT PATHWAY aCTD: 28-day attenuated cycles of cyclophosphamide (C) 500 mg os d 1, 8, 15, 22; thalidomide (T) 50 mg (increasing to 200 mg as tolerated) os daily; and dexamethasone (D) 20 mg os d 1–4, 15–18 aCRD: 28-day attenuated cycles of cyclophosphamide (C) 500 mg os d 1, 8; lenalidomide (R) 25 mg os d 1–21; and dexamethasone (D) 20 mg os d 1–4, 15–18. BOTH TREATMENT PATHWAYS Suboptimal responders (<VGPR) not receiving KCRD received intensification with bortezomib plus dexamethasone and cyclophosphamide (VCD). Eligible patients who completed induction therapy according to the protocol received maintenance treatment with lenalidomide or no maintenance.	2568 1852	68 (60-74)

Abbreviations. N, number; IQR, interquartile range; PD, progressive disease; os, oral administration; iv, intravenous administration; sc, subcutaneous administration; d, day; MEL200, melphalan at 200 mg/m^2; ASCT, autologous stem-cell transplantation; CR, complete response; a-, attenuated; VGPR, very good partial response; ID, identifier; No., register number.

Table S3. Performances of the possible cut-offs according to different grouping strategies

The cut-offs with the highest C-index were selected for grouping.

Group cut-offs	C-index estimate at 60 months	Smallest group proportion, % of the total training set	5-year OS of the high-risk group, %
0 / 0.5-1 / 1.5-2.5 / 3-5	**0.7227**	**8.76%**	**36.95%**
0 / 0.5-1.5 / 2-2.5 / 3-5	0.7214	8.76%	36.95%
0-0.5 / 1 / 1.5-2.5 / 3-5	0.7146	8.76%	36.95%
0-0.5 / 1-1.5 / 2-2.5 / 3-5	0.7095	8.76%	36.95%
0-1 / 1.5 / 2-2.5 / 3-5	0.7083	8.76%	36.95%

Abbreviations. OS, overall survival.

Table S4. IPCW method to estimate the C-index according to the R2-ISS and R-ISS

Patient population	Risk score	C-index estimate at 60 months	C-index estimate at 90 months	C-index estimate at 120 months
Training set	R2-ISS	72.3	70.6	70
Training set	R-ISS	73.1	71.5	70.6
Validation set	R2-ISS	71.2	69.6	NA
Validation set	R-ISS	68.2	68.0	NA

Abbreviations. IPCW, inverse probability of censoring weighted; R2-ISS, Second Revision of the International Staging System; R-ISS, Revised International Staging System; NA, not available.

Table S5. R-ISS distribution according to the R2-ISS in evaluable patients included in the training set (N=2226)

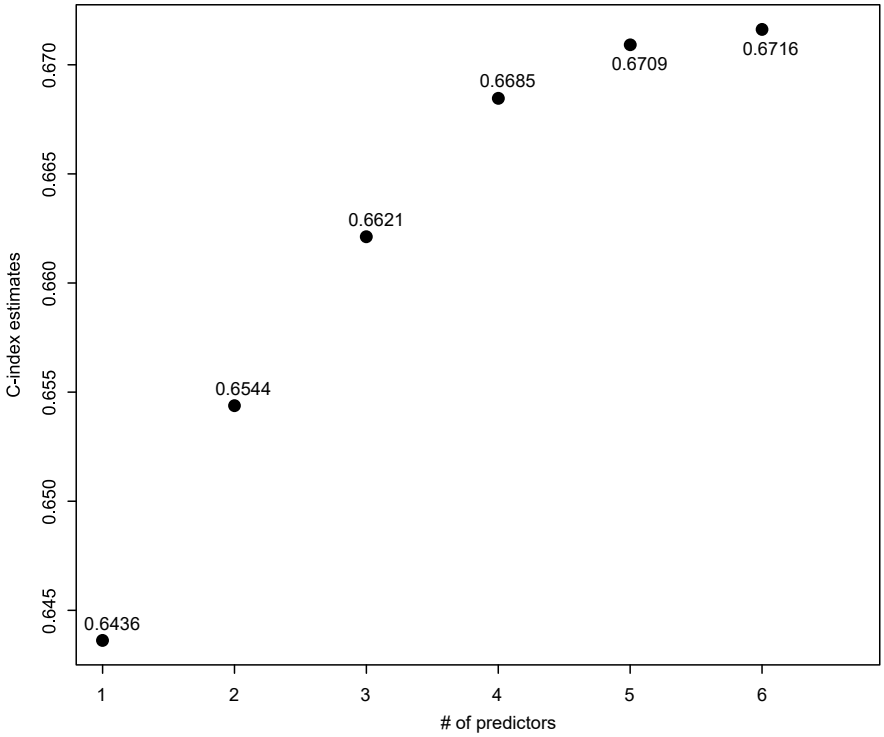
Prognostic score	R2-ISS low (I, N=428)	R2-ISS low-int (II, N=686)	R2-ISS int-high (III, N=917)	R2-ISS high (IV, N=195)
R-ISS I	428	169	0	0
R-ISS II	0	517	811	44
R-ISS III	0	0	106	151

Abbreviations. R-ISS, Revised International Staging System; R2-ISS, Second Revision of the International Staging System; N, number; int, intermediate.

Supplementary figures

Figure S1. C-index estimates according to the number of features included in the R2-ISS score calculation

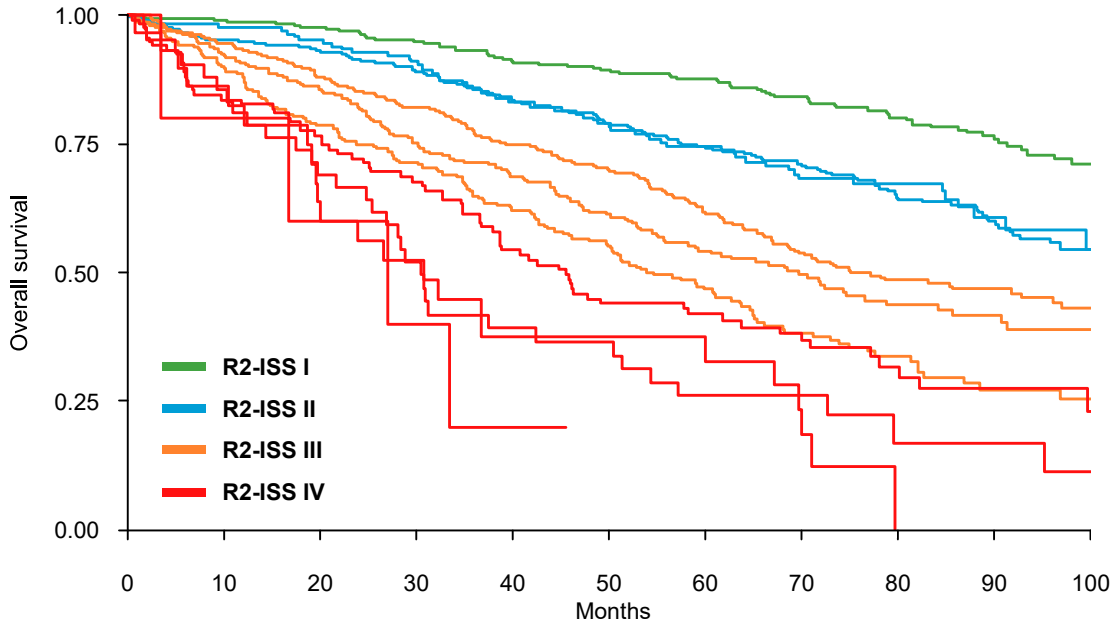
C-index estimates defined using the inverse probability of censoring weighted (IPCW) method at 60 months are shown.



Abbreviations. R2-ISS, Second Revision of the International Staging System.

Figure S2. OS according to the continuous score calculation

Each curve represents a 0.5 score point. Curves of the same color were grouped together in the final R2-ISS model.

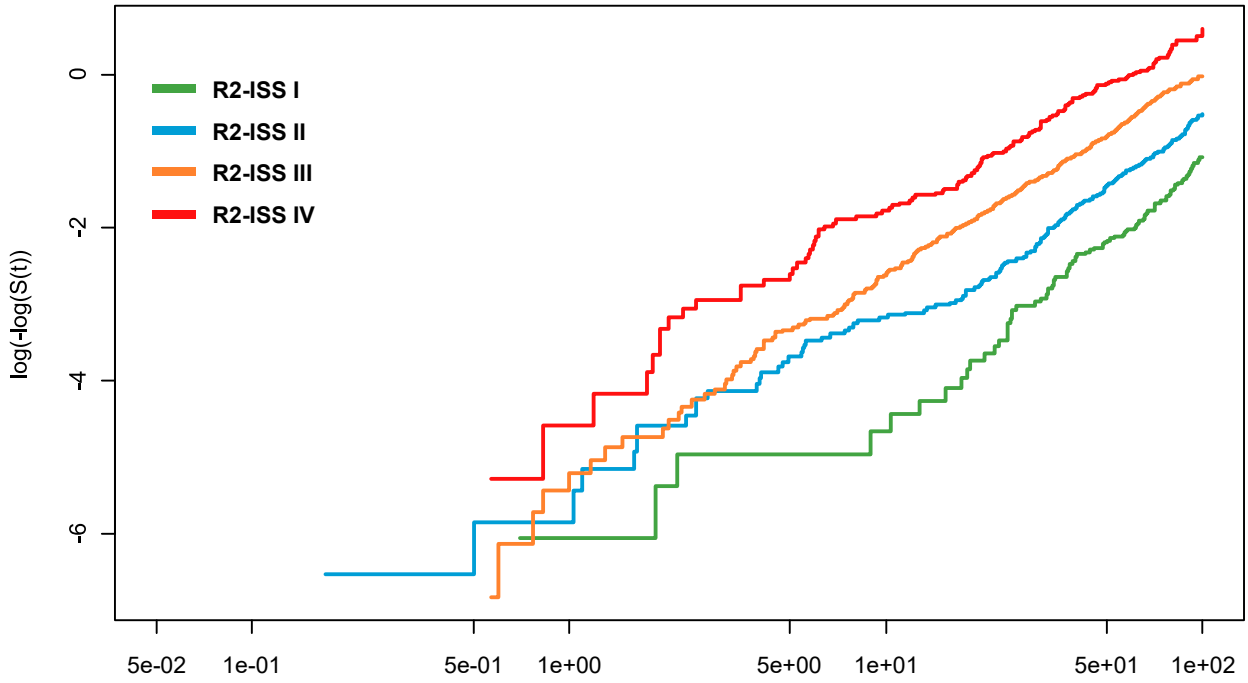


Abbreviations. OS, overall survival; R2-ISS, Second Revision of the International Staging System.

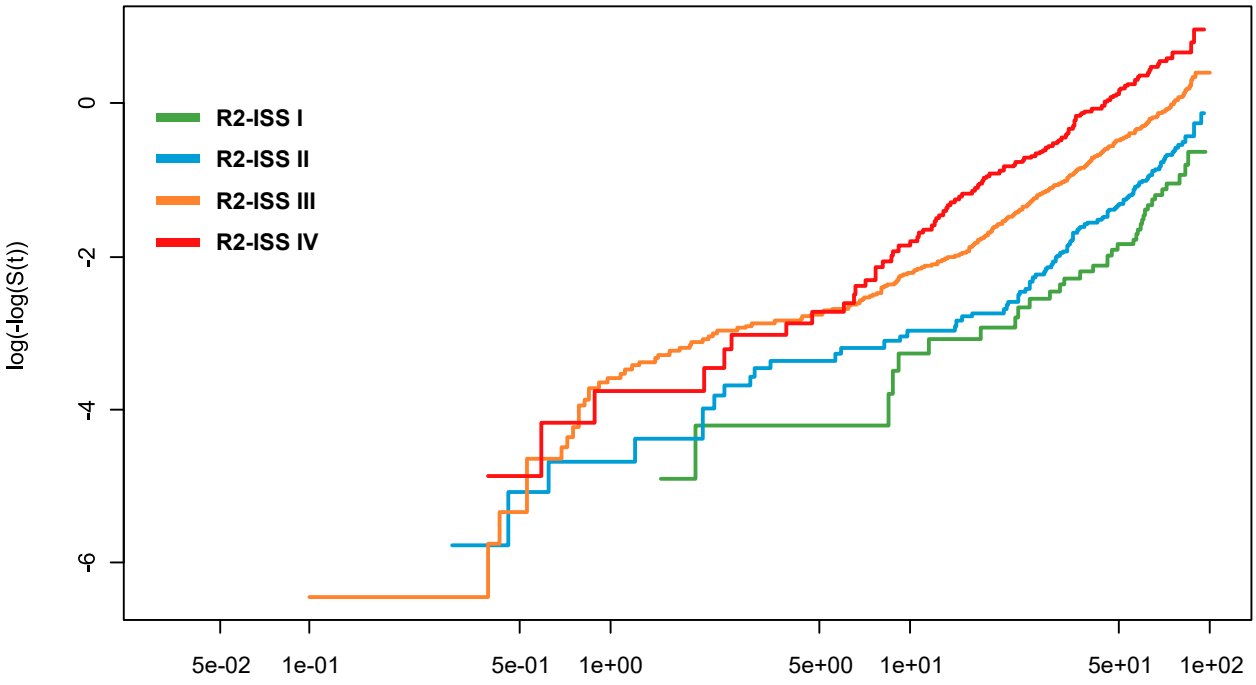
Figure S3. Proportional hazards assessment of the R2-ISS for OS

A log-negative log plot by R2-ISS risk group for OS was performed in the training (Panel a) and validation (Panel b) sets as a visual approach to evaluate the proportional hazards assumption.

S3a. Log-negative log plot by R2-ISS risk group for OS in the training set



S3b. Log-negative log plot by R2-ISS risk group for OS in the validation set

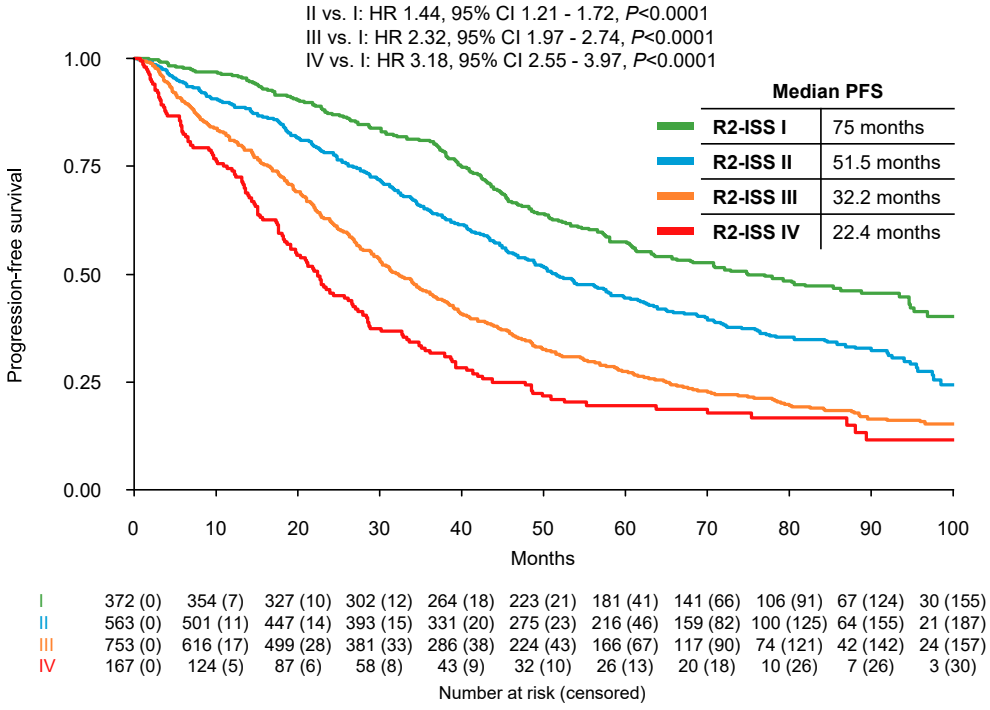


Abbreviations. R2-ISS, Second Revision of the International Staging System; OS, overall survival.

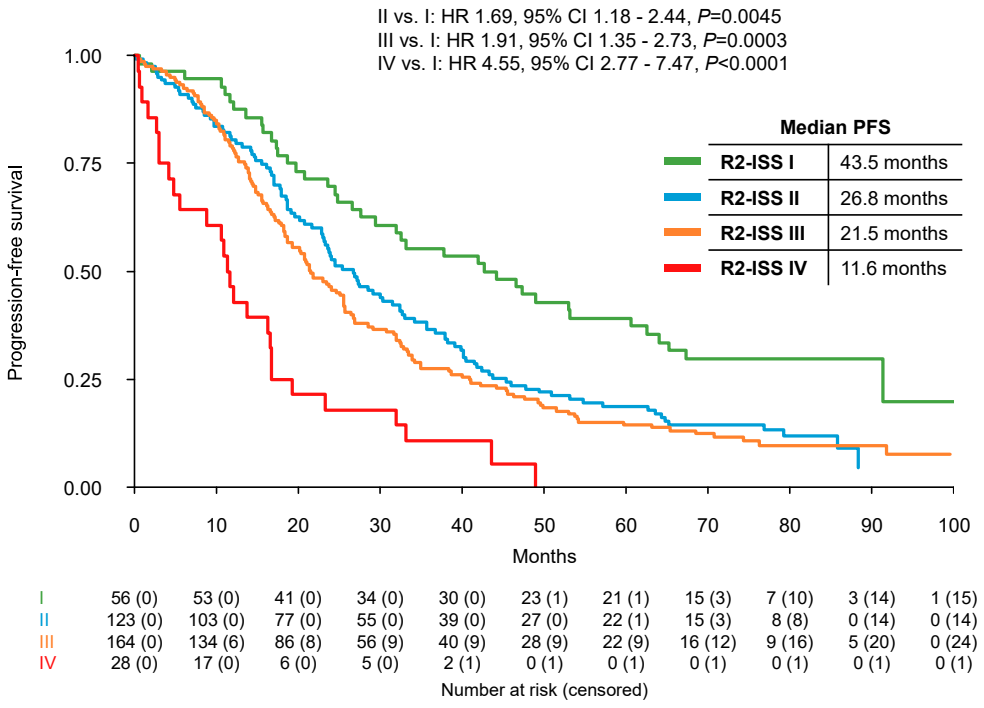
Figure S4. R2-ISS and PFS by transplant eligibility and type of treatment in the training set

Panel a refers to progression-free survival (PFS) in transplant-eligible patients; Panel b refers to PFS in transplant-ineligible patients; Panel c refers to PFS in patients receiving regimens based on immunomodulatory drugs (IMiDs); Panel d refers to PFS in patients receiving regimens based on proteasome inhibitors (PIs); and Panel e refers to PFS in patients receiving regimens based on IMiDs plus PIs.

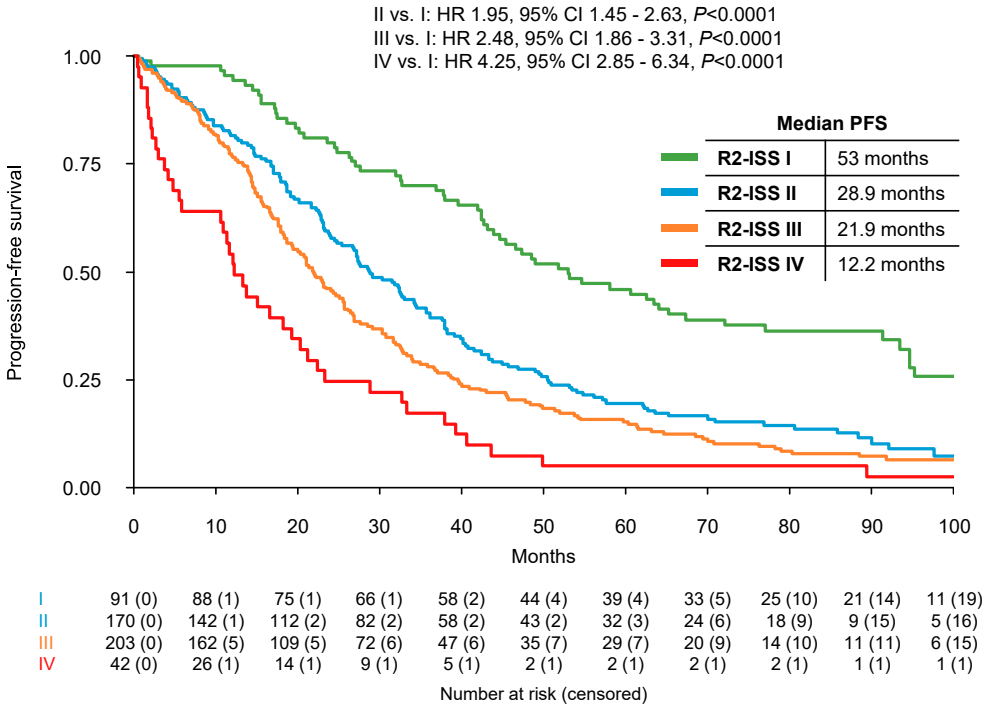
S4a. PFS in transplant-eligible patients



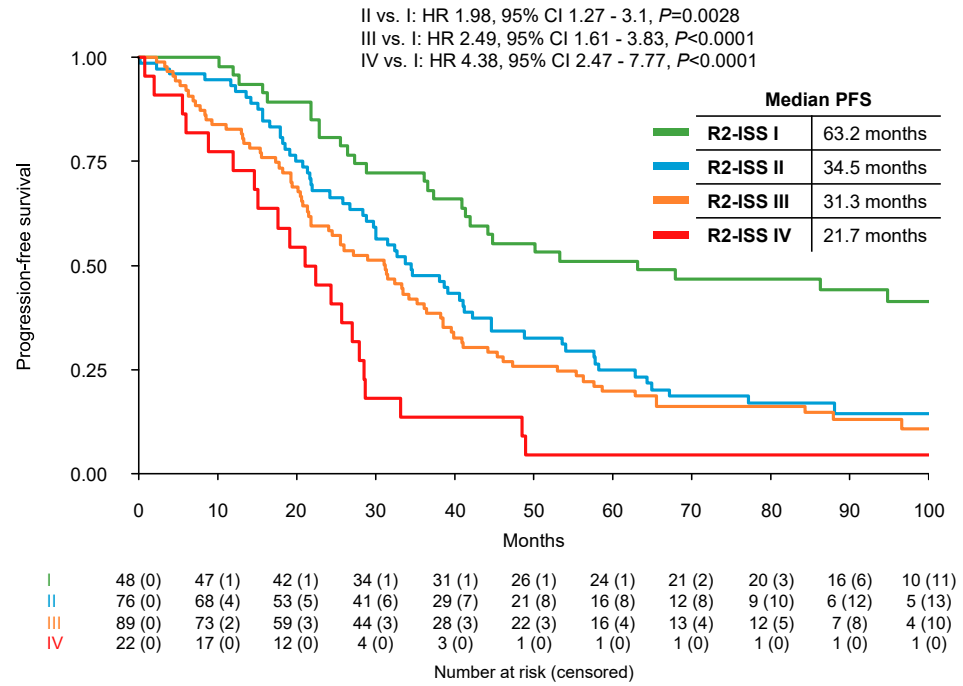
S4b. PFS in transplant-ineligible patients



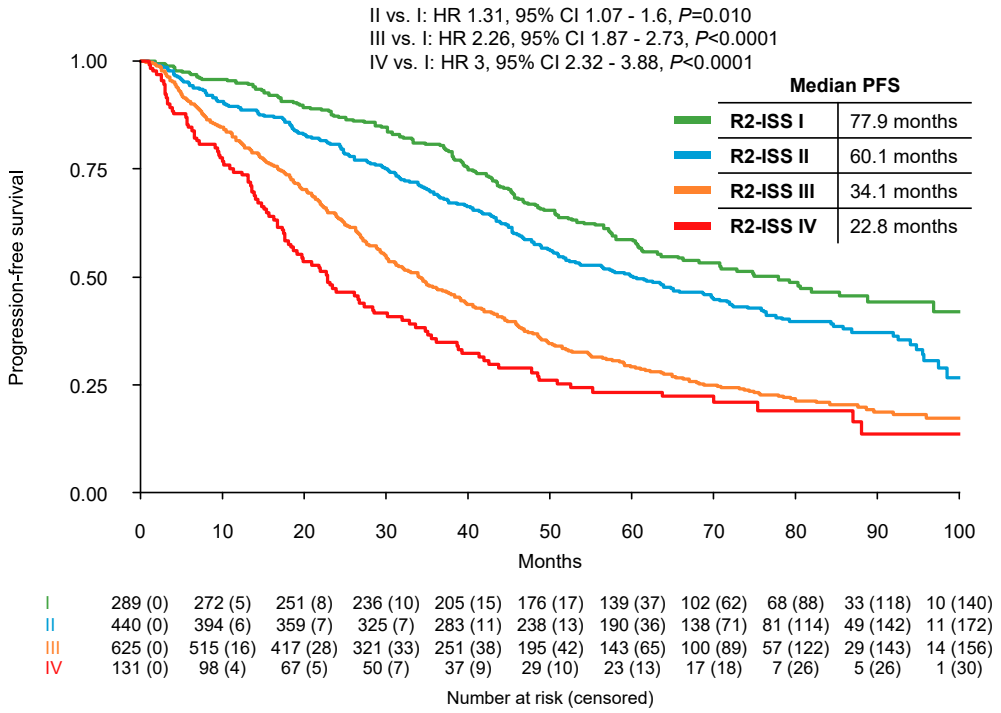
S4c. PFS in patients receiving IMiD-based regimens



S4d. PFS in patients receiving PI-based regimens



S4e. PFS in patients receiving IMiD plus PI-based regimens

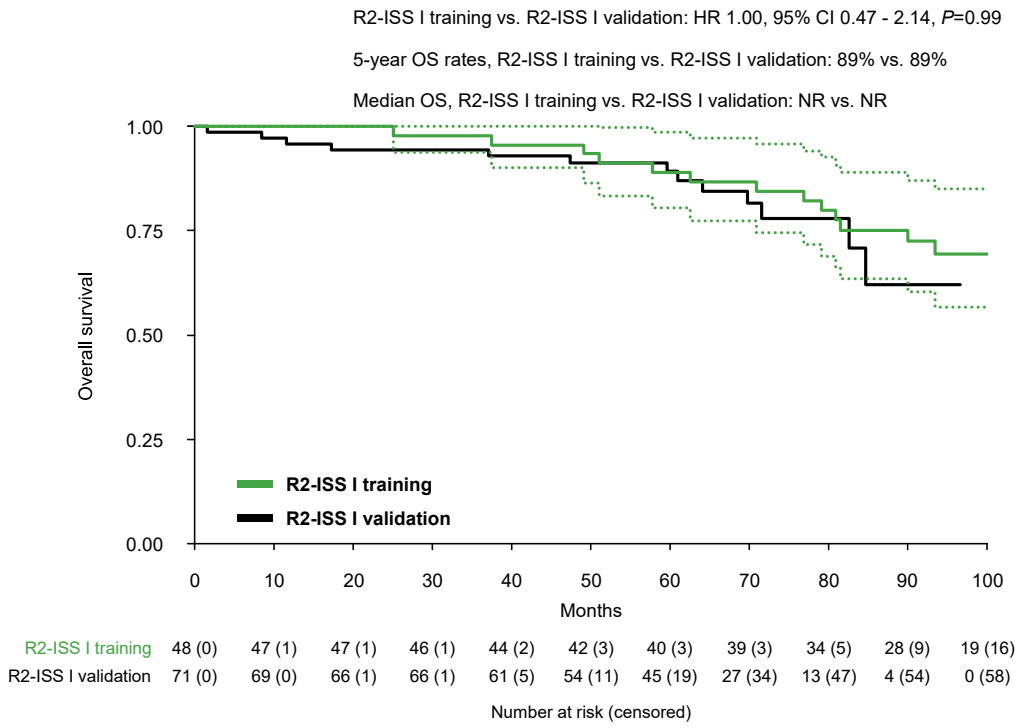


Abbreviations. R2-ISS, Second Revision of the International Staging System; PFS, progression-free survival; IMiDs, immunomodulatory drugs; PIs, proteasome inhibitors; HR, hazard ratio; CI, confidence interval; *P*, p-value; NR, not reached.

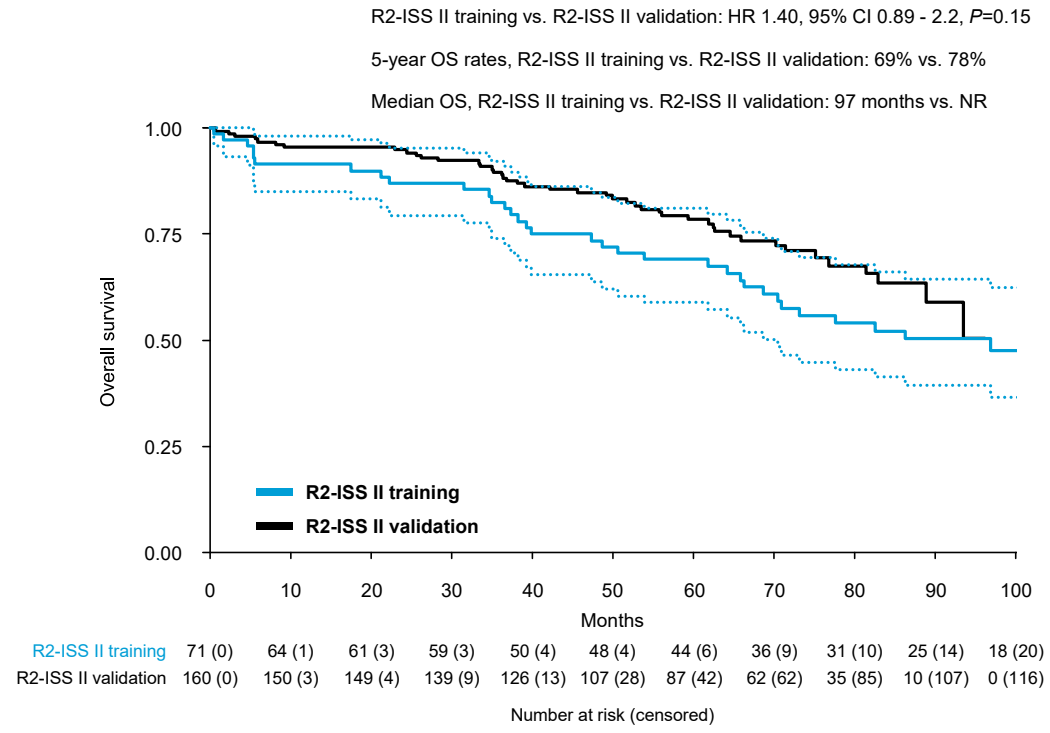
Figure S5. Calibration of the R2-ISS in transplant-eligible patients receiving an IMiD-based treatment

In each panel, the comparison between the same R2-ISS-defined risk subgoup in the training set vs. validation set is shown. Dotted lines refer to the 95% conficence interval of the survival curve in the training set.

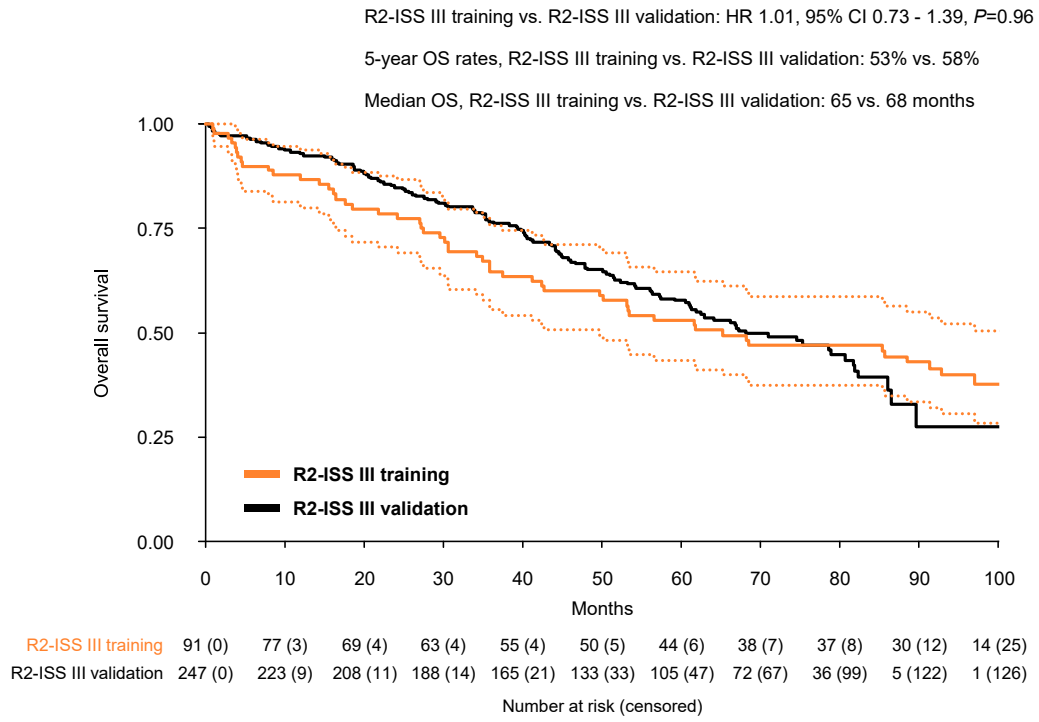
S5a. R2-ISS I



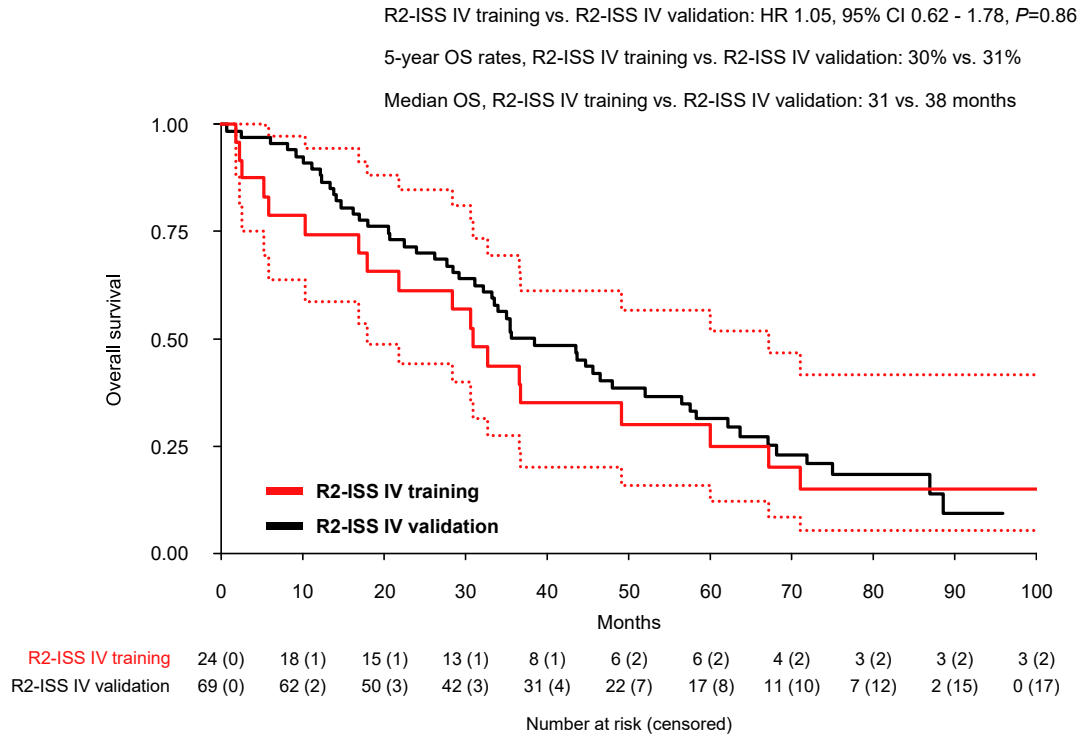
S5b. R2-ISS II



S5c. R2-ISS III



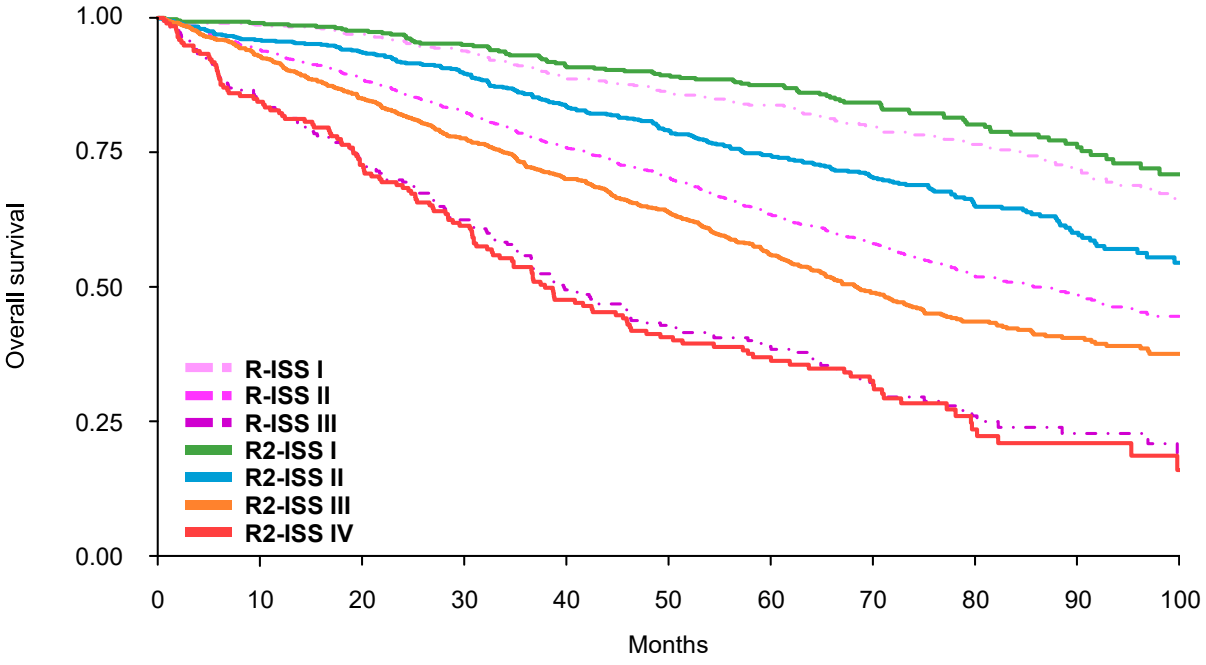
S5d. R2-ISS IV



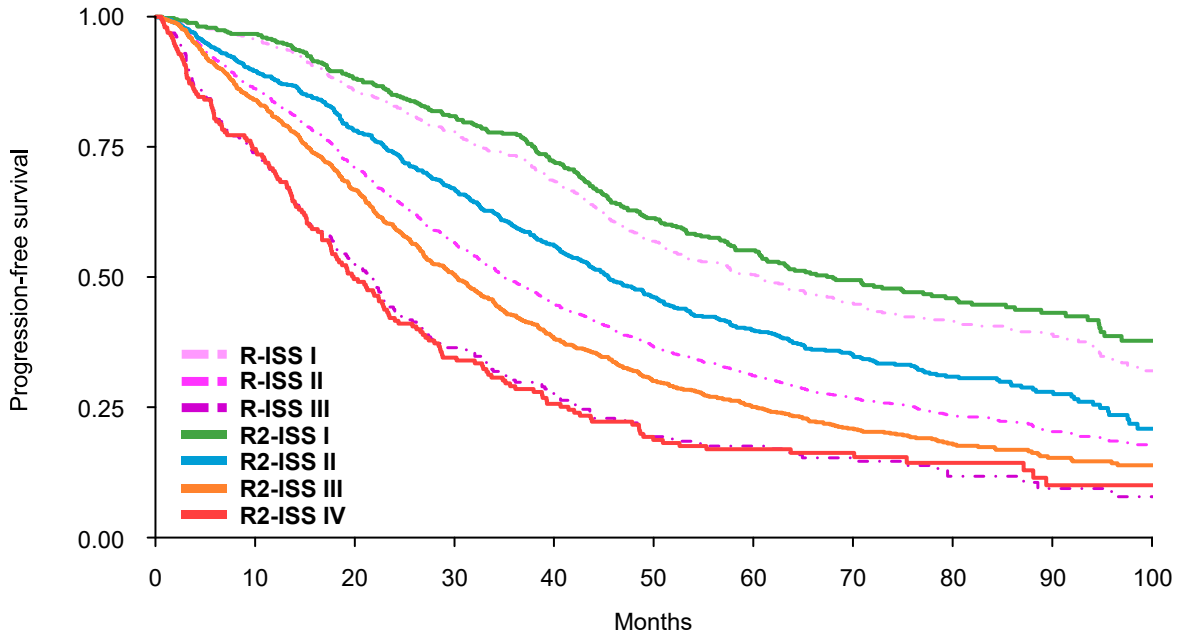
Abbreviations. R2-ISS, Second Revision of the International Staging System; IMiD, immunomodulatory drug; HR, hazard ratio; CI, confidence interval; *P*, p-value; OS, overall survival; NR, not reached.

Figure S6. OS (Panels a, c) and PFS (Panels b, d) curves in the training (Panels a-b) and validation (Panels c-d) sets according to the R2-ISS, with superimposed R-ISS in the same patient population

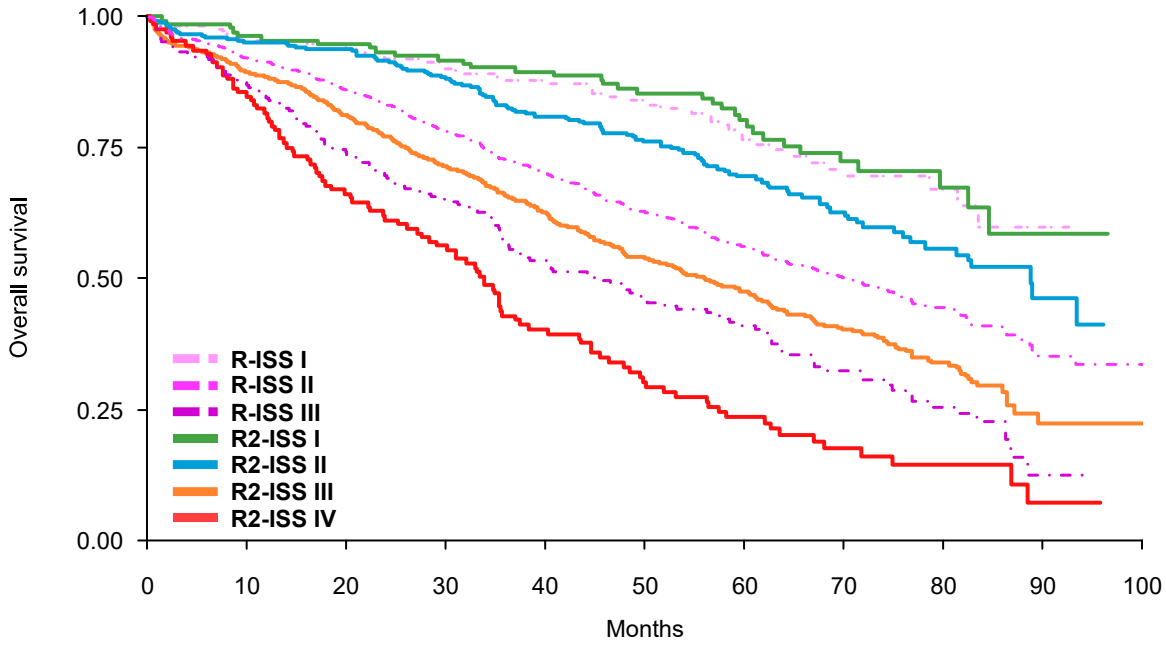
S6a. OS - Training set



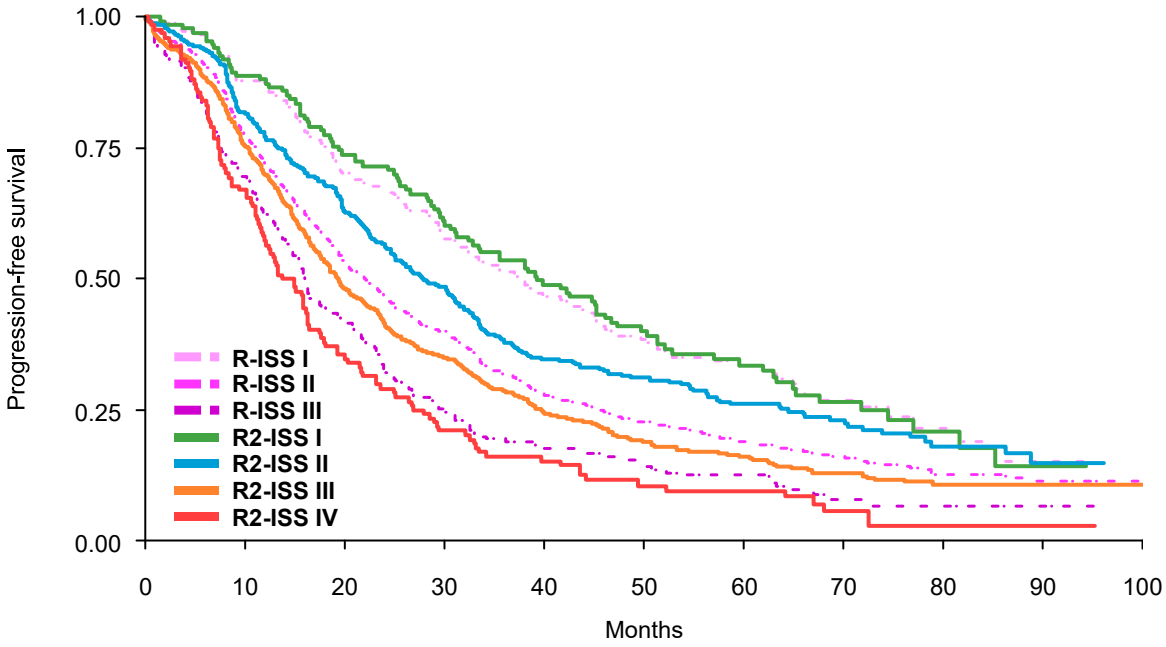
S6b. PFS - Training set



S6c. OS - Validation set



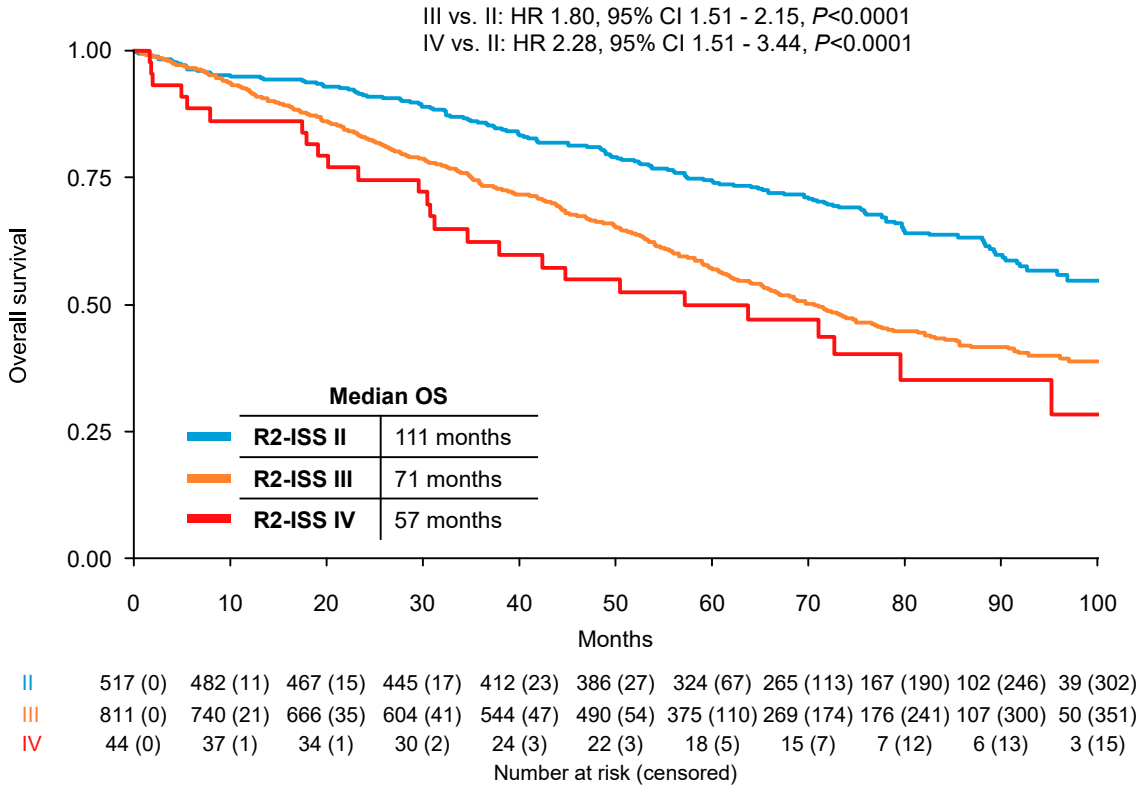
S6d. PFS - Validation set



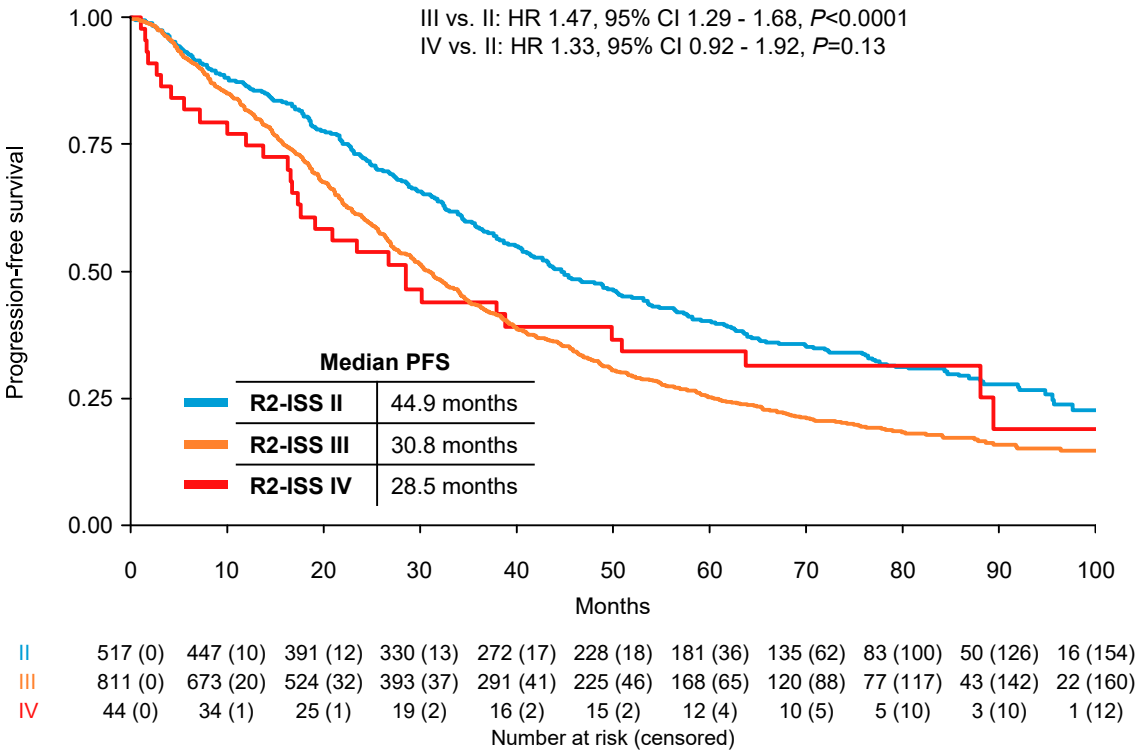
Abbreviations. OS, overall survival; PFS, progression-free survival; R2-ISS, Second Revision of the International Staging System; R-ISS, Revised International Staging System.

Figure S7. OS (Panels a, c) and PFS (Panels b, d) of R-ISS II patients according to the R2-ISS in the training (Panels a-b) and validation (Panels c-d) sets

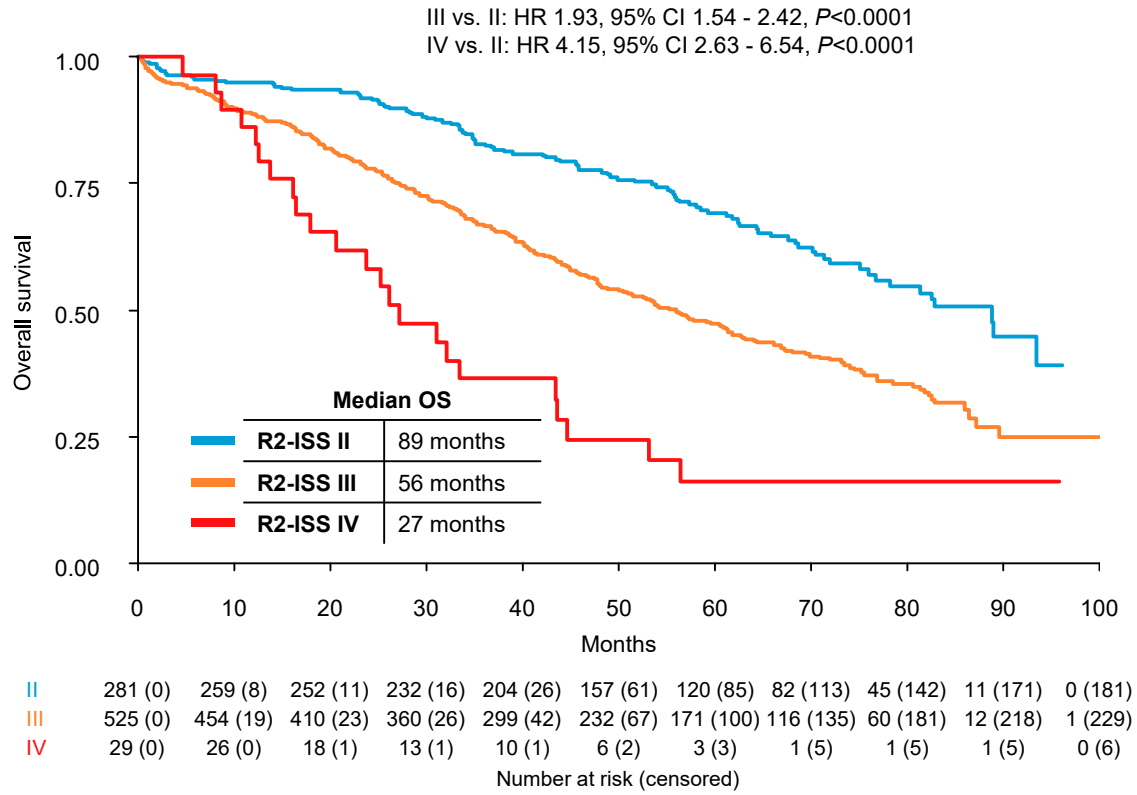
S7a. OS - Training set



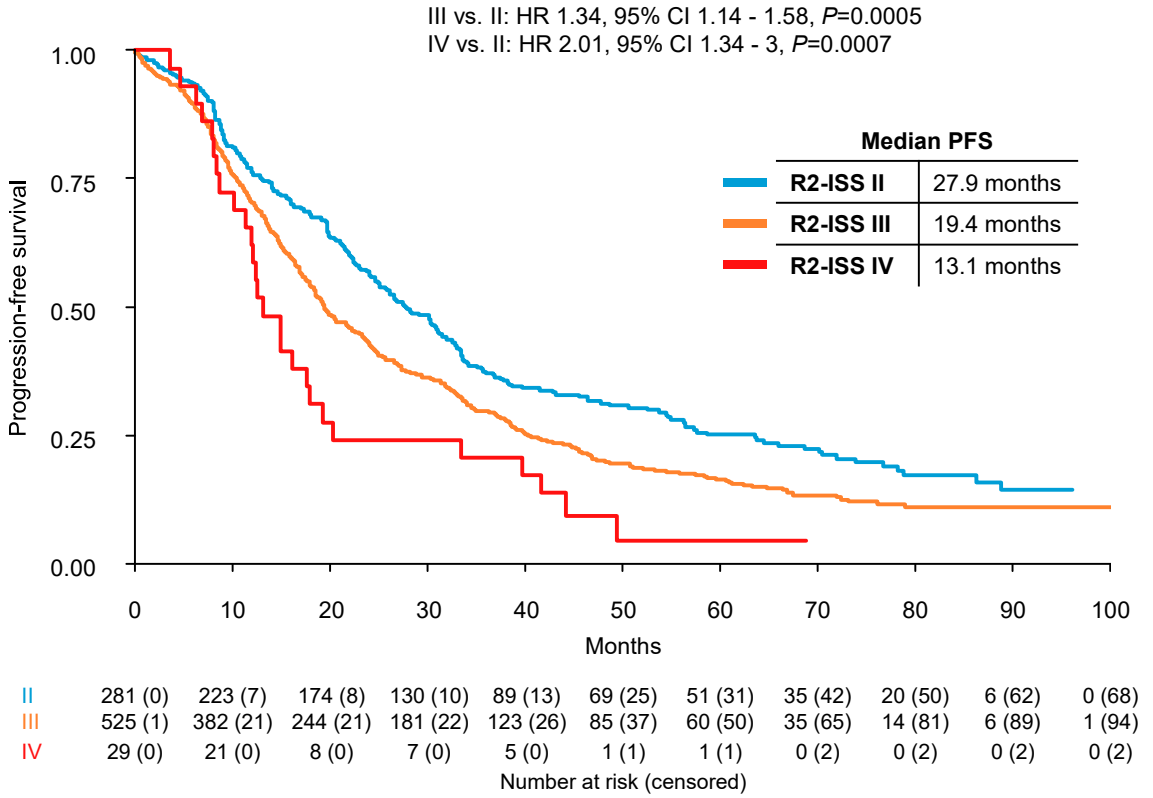
S7b. PFS - Training set



S7c. OS - Validation set

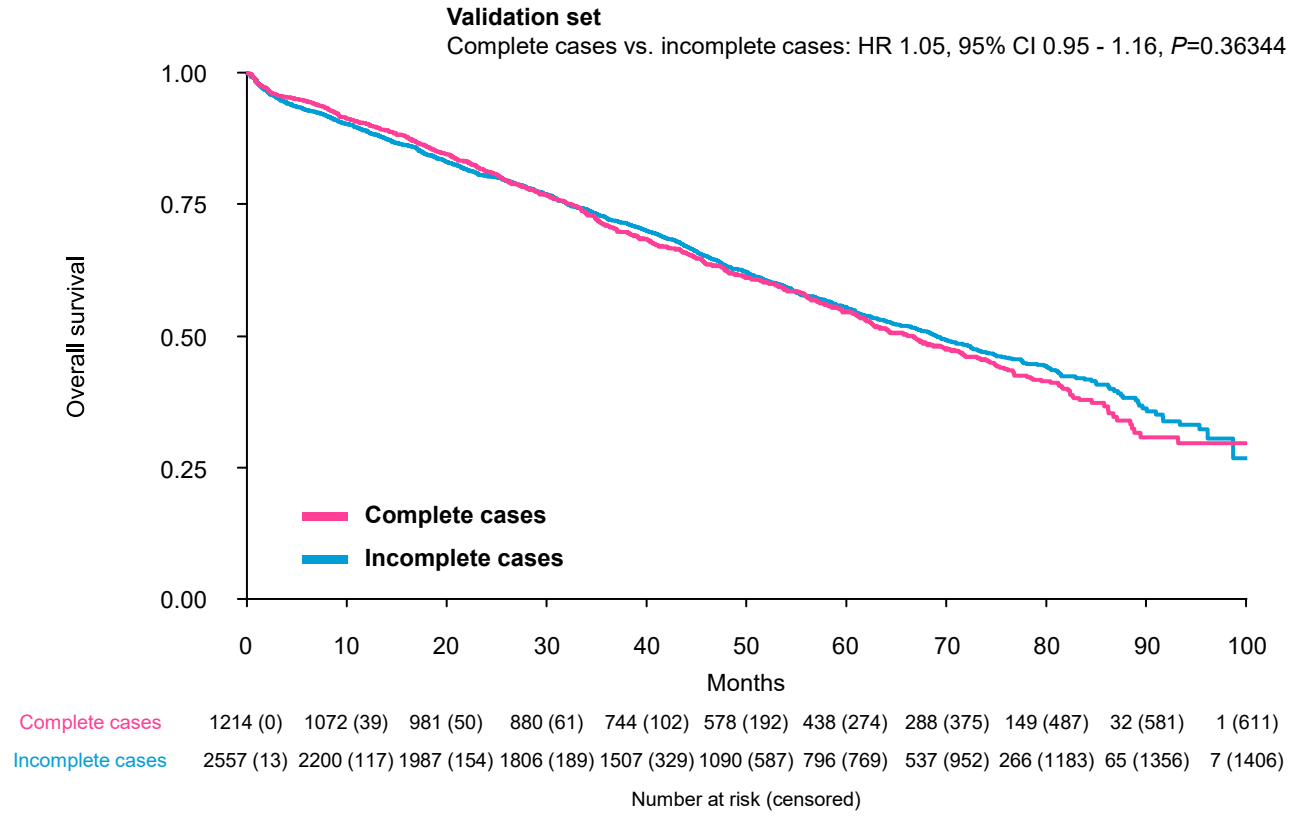


S7d. PFS - Validation set



Abbreviations. OS, overall survival; PFS, progression-free survival; R-ISS II, Revised International Staging System stage II; R2-ISS, Second Revision of the International Staging System; HR, hazard ratio; CI, confidence interval; *P*, p-value.

Figure S8. OS in complete vs. incomplete cases in the validation set



Abbreviations. OS, overall survival; HR, hazard ratio; CI, confidence interval; *P*, p-value.

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